Cover page

Official Title:

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

ClinicalTrials.gov identifier:

NCT03742037

Date of document:

27 September 2022

CENERIMOD (ACT-334441)

STATISTICAL ANALYSIS PLAN

FOR CLINICAL STUDY REPORT

ID-064A202

CARE: Cenerimod **A**ssessing S1P1 **R**eceptor modulation in Systemic Lupus **E**rythematosus

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

Document Number: D-22.294

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LIST OF ABBREVIATIONS AND ACRONYMS

ACR	American College of Rheumatology
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike's Information Criterion
anti-dsDNA	Anti-double-stranded deoxyribonucleic acid
ATC	Anatomical Therapeutic Chemical
BILAG(-200)4	British Isles Lupus Assessment Group(-2004)
BMI	Body mass index
BP	Bodily pain
bpm	Beats per minute
CARE	**C**enerimod **A**ssessing $S1P_1$ **R**eceptor modulation in Systemic Lupus **E**rythematosus
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
CRO	Contract Research Organization
CSR	Clinical study report
CV	Coefficient of variation
DBP	Diastolic blood pressure
DV	Protocol deviation
ECG	Electrocardiogram/graphy
(e)CRF	(Electronic) case report form
ECS	Echocardiography Set
E_{max}	Maximum effect
EOS	End-of-Study
EOT	End-of-Treatment
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full Analysis Set Treatment Period 1
FEV_1	Forced expiratory volume in 1 second
FU	Follow-up

FVC	Forced vital capacity
GH	General health
GLMM	Generalized linear mixed model
HIV	Human immunodeficiency virus
HLGT	High-level group term
HR	Heart rate
ICH	International Council for Harmonisation
IgA/G/M	Immunoglobulin A/G/M
IXRS	Interactive Response System
linlog	Linear in log
LSM	Least Square Means
MAR	Missing at random
MCMC	Markov chain Monte Carlo
MCP	Multiple comparison procedures
MCS	Mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mental health
MMRM	Mixed model for repeated measures
MNAR	Missing not at random
Mod	Modeling
(m)SLEDAI-2K	(Modified) Systemic Lupus Erythematosus Disease Activity Index-2000
OCS	Oral corticosteroids
OR	Odds ratio
PCS	Physical component summary
PF	Physical functioning
PGA	Physician's Global Assessment
PGIC-F	Patient Global Impression of Change – Fatigue
PGIS-F	Patient Global Impression of Severity – Fatigue

PK	Pharmacokinetic(s)
PKS	Pharmacokinetic Analysis Set
PPS	Per-Protocol Set
PRO	Patient-reported outcome
PT	Preferred term
QoL	Quality of life
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RE	Role-emotional
RP	Role-physical
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SCR	Screened Analysis Set
SDTM	Study Data Tabulation Model
SF	Social functioning
SF-36v2	36-Item Short Form Health Survey version 2
SI	Standard International
SLE	Systemic lupus erythematosus
SMQ	Standardised MedDRA Query
SOC	System organ class
SRI	Systemic Lupus Erythematosus Responder Index
TEAE	Treatment-emergent adverse event
TP1	Treatment Period 1
TP2	Treatment Period 2
US	United States
VT	Vitality
WHO	World Health Organization

1 INTRODUCTION

This SAP for the clinical study report for study ID-064A202 (CARE) is based on global protocol Version 5, 4 February 2022 [D-22.031]. The SAP describes analyses of the primary, secondary, other, and exploratory efficacy endpoints as well as all safety, QoL, PK, and biomarker endpoints.

Source data for the analyses will be provided as SAS® datasets in SDTM format following CDISC. Analysis data sets will be derived as SAS® data sets in Analysis Data Model format following CDISC.

The clinical pharmacologist will perform the calculation of PK parameters and create figures of individual and mean concentration-time profiles. PK concentration data will be merged with the actual date/time of sampling by Idorsia Data Management.

Table 1 summarizes the study committees involved during the conduct of the study.

Table 1 Study committees

Committee	Responsibility
Independent Data Monitoring Committee	Review of safety data and provision of recommendations on trial continuation and conduct.
Ophthalmology Safety Board	Review and adjudication of all data related to cases suggestive of macular edema.

2 STUDY DESIGN AND FLOW

2.1 Study design

This is a Phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy, safety, and tolerability of cenerimod in subjects with moderate to severe SLE.

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

Once randomized, all subjects will enter a 6-month double-blind study treatment period defined as Treatment Period 1 (TP1).

Subjects randomized to, and still receiving, placebo, 0.5, 1, or 2 mg at Month 6 will continue their study treatment up to an additional maximum of 6 months in Treatment Period 2 (TP2), for a total maximum of 12 months.

Subjects randomized to the 4 mg arm will receive study treatment at this dose for a maximum of 6 months in TP1. Afterwards, subjects in this group, still receiving this dose

at Month 6, will be re-randomized in a 1:1 ratio to placebo or cenerimod 2 mg to enter TP2 and will continue for a total maximum of 12 months

Subjects who discontinue treatment in TP1 will continue study FU, performing study assessments, up to maximum duration of 12 months.

At EOT, subjects will enter a 6-month FU period (4-month before protocol Version 5).

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

The study will be conducted at approximately 180 sites in 21 countries notably from the regions of Asia Pacific, Eastern Europe, Latin America, North America, and Western Europe.

No interim analysis is planned. There will be three study analyses: the Month-6 analysis, the Month-12 analysis and the final EOS analysis. Month-6 analysis will be performed when all randomized subjects have completed TP1 or discontinued the study. Month-12 analysis will be performed when all randomized subjects have completed TP2 or discontinued the study. Final EOS analysis will be performed when all randomized subjects have completed the post-treatment follow-up period or discontinued the study.

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

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

2.1.1 Echocardiography ancillary study

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

2.2 Study visit and assessment schedule

See Appendix 12.1 for the visit and assessment schedule.

2.3 Study periods

2.3.1 Screening period

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

During this period, the subject's SLE background medication should be maintained stable except for OCS which should be tapered to the minimum required dose and maintained stable for at least 15 days prior to Randomization [see protocol section 5.2.2.1, D-22.031].

2.3.2 Treatment periods

The study comprises 2 treatment periods: TP1 and TP2.

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

Starting at the Month 6 visit, TP2 lasts for up to 6 months and ends at the Month 12 visit.

If a randomized subject discontinues treatment prematurely in TP1 or TP2, the subject will have a premature EOT visit, stay in the study, and complete all protocol-mandated visits up to the Month 12 visit (unless the subject withdraws consent earlier).

At the time of the Month 12 visit, the EOT visit will take place.

Furthermore, at this time the EOS visit will take place for subjects with premature EOT occurring at least 6 months prior to the Month 12 visit. For subjects with premature EOT occurring less than 6 months prior to the Month 12 visit, the 6-month FU period must be completed in its entirety. For example, if a subject has premature EOT at Month 8 occurring four months prior to the Month 12 visit, Month 9, Month 10, Month 11 and Month 12 visits, also functioning as FU1, FU2, FU3, and FU3a, are conducted as planned, along with FU3b and EOS visits after the Month 12 visit. This completes 6 months of follow-up.

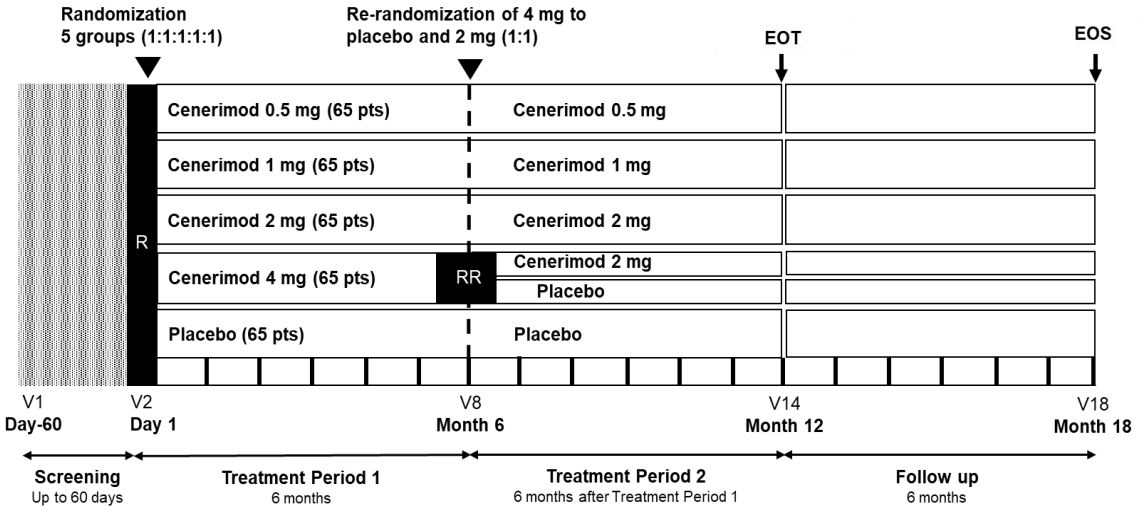
2.3.3 Follow-up period

This period starts after the EOT visit and lasts 6 months until the EOS visit.

For the first 5 months after the EOT visit, subjects will have to conduct monthly FU visits or phone calls at FU1, FU2, FU3, FU3a, and FU3b, to collect information on AEs/SAEs and/or pregnancy. For subjects that discontinue treatment prematurely, some or all FU visits may be replaced by scheduled visits.

EOS should occur 6 months after the EOT but can occur later for subjects that prematurely discontinue treatment before Month 8. Study periods are displayed in Figure 1.

Figure 1 Study design ID-064A202 (CARE)



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

2.4 Overview of analysis periods

2.4.1 Analysis periods for primary efficacy endpoint, secondary efficacy endpoints and other efficacy endpoints

Primary, secondary, and other efficacy endpoints as well as PRO and QoL endpoints will be analyzed from start of treatment up to the Month 6 assessment during TP1.

2.4.2 Analysis periods for exploratory endpoints

Exploratory and PRO endpoints will be analyzed from baseline up to a maximum of 12 months on all available assessments according to the following 2 groups [as defined in the protocol, D-22.031]:

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

The exploratory endpoints will be analyzed from first study drug intake in TP1 up to the Month 12 assessment (pooling TP1 and TP2 data), as well as from re-randomization (in TP2) at Month 6 up to the Month 12 assessment.

2.4.3 Analysis periods for safety and biomarker endpoints

Safety and biomarker endpoints will be analyzed from start of treatment in TP1 up to the Month 6 assessment, from start of treatment in TP2 up to the Month 12 visit, and from start of treatment in TP1 up to the Month 12 visit (pooling TP1 and TP2 data).

3 OBJECTIVES

3.1 Primary objective

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

3.1.1 Estimands

The three estimands for the primary objective of this study are defined by the five attributes as shown in Table 2 and specified in ICH E9 (R1).

Table 2 Estimands for the primary objective

Estimand	Target population	Treatment condition of interest	Endpoint	Strategy for addressing intercurrent events	Population-level summary
Primary Estimand	Adult subjects with moderate to severe SLE concurrently receiving background therapy as defined by the inclusion and exclusion criteria in the study protocol.	Cenerimod 0.5 mg, 1 mg, 2 mg and 4 mg plus background SLE therapy which will be compared to placebo plus background SLE therapy.	Change from baseline to Month 6 in the mSLEDAI-2K score (primary endpoint).	Treatment policy, i.e., all collected endpoint data are used regardless of early treatment discontinuation or other intercurrent events. Missing data will be handled as described in Section 7.2.3.	Mean change from baseline to Month 6, summarized as the difference between cenerimod treatment given at 4 different dose levels (0.5, 1, 2 and 4 mg) and placebo.
Secondary Estimand #1	Adult subjects with moderate to severe SLE concurrently receiving background therapy as defined by the inclusion and exclusion criteria in the study protocol.	Cenerimod 0.5 mg, 1 mg, 2 mg and 4 mg plus background SLE therapy which will be compared to placebo plus background SLE therapy.	Response at Month 6 on SRI-4 (secondary endpoint).	Treatment policy, i.e., all collected endpoint data are used regardless of early treatment discontinuation or other intercurrent events. Missing data will be handled as described in Section 7.3.1.3.	Proportion of responders at Month 6, summarized as the ratio between cenerimod treatment given at 4 different dose levels (0.5, 1, 2 and 4 mg) and placebo.
Secondary Estimand #2	Adult subjects with moderate to severe SLE concurrently receiving background therapy as defined by the inclusion and exclusion criteria in the study protocol.	Cenerimod 0.5 mg, 1 mg, 2 mg and 4 mg plus background SLE therapy which will be compared to placebo plus background SLE therapy.	Response at Month 6 on BILAG-2004 (secondary endpoint).	Treatment policy, i.e., all collected endpoint data are used regardless of early treatment discontinuation or other intercurrent events. Missing data will be handled as described in Section 7.3.2.3.	Proportion of responders at Month 6, summarized as the ratio between cenerimod treatment given at 4 different dose levels (0.5, 1, 2 and 4 mg) and placebo.

BILAG-2004 = British Isles Lupus Assessment Group-2004; mSLEDAI-2K = modified Systemic Lupus Erythematosus Disease Activity Index-2000; SLE = systemic lupus erythematosus; SRI = Systemic Lupus Erythematosus Responder Index.

3.2 Secondary objectives

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

- The safety and tolerability of cenerimod treatment.
- The effect of cenerimod treatment on QoL and fatigue using relevant PRO instruments.
- The effect of cenerimod treatment on SLE biomarkers.

3.3 Exploratory objectives

To explore the sustainability of the treatment effect, further objectives are assessed over a treatment period of up to 12 months:

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

4 ANALYSIS SETS

4.1 Definitions of analysis sets

4.1.1 Screened Analysis Set

The SCR includes all subjects who entered Screening and have a subject identification number.

4.1.2 Full Analysis Set

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

4.1.3 Full Analysis Set - TP2

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

4.1.4 Per-Protocol Set

The PPS includes all subjects from the FAS without clinically important DVs occurring during TP1 which could affect the analysis of the primary endpoint variable.

The precise reasons for excluding subjects from the PPS will be fully defined and documented in a separate document before breaking the randomization blind.

The PPS will only be defined for the period TP1.

4.1.5 Safety Analysis Set

The SAF includes all subjects who received at least one dose of double-blind study treatment during TP1. Subjects will be analyzed based on the treatment received. In the event of accidental intake of a treatment other than the randomized treatment, treatment received is defined as the highest dose received.

4.1.6 Safety Analysis Set - TP2

The SAF-TP2 includes all subjects from the SAF who received at least one dose of double-blind study treatment during TP2. Subjects will be analyzed based on the treatment received. In the event of accidental intake of a treatment other than the randomized treatment during TP2, treatment received is defined as the highest dose received.

4.1.7 Echocardiography Set

The ECS includes subjects who were assigned to the echocardiography sub-study by IXRS with at least one post-baseline echocardiography assessment. Subjects will be analyzed based on the treatment received. In the event of accidental intake of a treatment other than the randomized treatment, treatment received is defined as the highest dose received.

4.1.8 PK Analysis Set

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

The reason for excluding a PK sample from analysis will be documented by Idorsia Clinical Pharmacology before breaking the randomization blind.

4.2 Usage of the analysis sets

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

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

The SAF will be used for the analysis of safety endpoints (including study treatment exposure) from TP1. SAF-TP2 will be used for specific analyses only including TP2 data. In the event of accidental intake of a treatment other than the randomized treatment occurring during TP2 while the treatment received during TP1 matched the randomized treatment, the subject will be analyzed under the actual treatment group during TP1 for safety analyses during TP1 only. Safety analyses during TP2 or TP1 and TP2 combined (and up to EOS) will use the highest dose received, as described in Section 4.1.

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

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

An overview of the different analysis sets is provided in Table 3.

Table 3 Overview of the different analysis sets and their usage

	Analysis sets				
Analyses / Data Displays	**SCR**	**FAS**	**PPS**	**SAF**	**PKS**
Screen failures, Analysis sets	X				
Protocol deviations		X			
Inclusion/exclusion criteria	X				
Subject disposition		X			
Demographics		X			
Baseline disease characteristics		X			
Medical history and current medical conditions		X			
SLE medical history		X			
SLE and previous and concomitant therapies		X			
Other screening assessments (physical exam, PGA, height, weight, smoking, chest X-ray, …)		X			
Study treatment exposure		X		X	
Efficacy: Primary endpoint		X	X		
Efficacy: Secondary endpoints		X	X		
Efficacy: Other endpoints		X			
Efficacy: Exploratory endpoints		X[a]			
Efficacy: Subgroup analyses		X			
PRO/QoL endpoints		X			
Pharmacokinetic endpoints					X
Safety endpoints				X[b]	
Biomarker endpoints		X			
All subject listings	X[c]	X[c]		X[c]	

Note: X: main analysis, (a): Exploratory efficacy endpoints will be analyzed using the FAS and/or FAS-TP2. (b): Safety endpoints will be analyzed using the SAF and/or SAF-TP2. (c): Some listings will not be produced using the SCR, because certain data will not be collected for screen failures.

FAS = Full Analysis Set; FAS-TP2 = Full Analysis Set in Treatment Period 2; PGA = Physician's Global Assessment; PKS = Pharmacokinetic Analysis Set; PPS = Per-Protocol Set; PRO = patient-reported outcome; QoL = quality of life; SAF = Safety Analysis Set; SAF-TP2 = Safety Analysis Set in TP2; SCR = Screened Analysis Set; SLE = systemic lupus erythematosus.

5 GENERAL DEFINITIONS AND DERIVATIONS

5.1 Study dates

The **'Date of informed consent'** is defined as the date at which the informed consent is signed by the subject. This date is collected on the Informed Consent eCRF page.

The **'Screening date'** is defined as the date where the subject was screened (visit date from IXRS subject eCRF page). If the subject was screened multiple times, the date of last screening attempt will be used.

The **'Randomization date'** is defined as the date when the subject was randomized to one of the four doses of cenerimod or placebo (at the start of TP1) and is taken from the IXRS subject eCRF page.

The **'Re-randomization date'** is defined as the date when the subject was re-randomized through the IXRS system. The re-randomization date is taken directly from this system. The re-randomization date will be populated for subjects who reach the Month 6 visit (on treatment) and are re-randomized.

Note: Subjects on 4 mg are re-randomized to placebo or 2 mg cenerimod in TP2. All other subjects are re-randomized to their original randomized group from TP1.

Definition of treatment start/end dates in TP1

- The **'Treatment start date (TP1)'** is defined as the date of the first study drug intake in TP1 (cenerimod or placebo), as documented in the eCRF Study Treatment Intake.
- The **'Treatment start time (TP1)'** is defined as the time on the date of the first study drug intake in TP1 (cenerimod or placebo), as documented in the eCRF Study Treatment Intake.
- The **'Treatment end date (TP1)'** is defined as the date of the last study drug intake in TP1 (cenerimod or placebo), as documented in the eCRF Study Treatment Log.

Definition of treatment start/end dates in TP2

Treatment start and end dates are defined in the same way as described for TP1.

Due to the start of a conflict in Ukraine around the same time as the planned EOT of several subjects in this country, sites had to stop their activities before entering the treatment end date for TP2 in the eCRF. This concerns a maximum of 9 subjects. For these subjects, the missing treatment end date for TP2 will be imputed at the start date of Month-12 visit. NB: This date is identical to the treatment completion date entered in the IRT system, except for one subject for whom it is the day after.

Overall EOT date

A subject's overall EOT date is defined as the latest of **Treatment end date (TP1)** and **Treatment end date (TP2).**

Re-initiation in TP1 (during first two weeks of treatment)

- The **'Date of re-initiation'** is defined as the date when the study treatment was re-initiated after a break of at least 7 days during the first two weeks of treatment in TP1. The date of re-initiation is taken from the Re-initiation / Study Drug Intake eCRF page. Only one re-initiation is permitted per subject during TP1.
- The **'Time of re-initiation'** is defined as the corresponding time recorded on the Re-initiation / Study Drug Intake eCRF page.

EOS date

- The **'EOS date'** is taken from the eCRF End-of-Study / Visit Summary form. If this date is missing, the last recorded (follow-up) visit or phone call on the eCRF is considered to be the EOS date.

5.2 Baseline

- The **'Baseline (TP1)'** value for **efficacy and safety analyses** is defined as the last non-missing value recorded prior to first study drug intake in TP1 for each endpoint and each subject individually. For subjects that were randomized but did not take any study drug, baseline (TP1) is defined as the last non-missing value recorded up to and including the day of Randomization.
- The **'Baseline (TP2)'** value for **efficacy and safety analyses** is defined as the last non-missing value recorded up to and including the day of re-randomization for each endpoint and each subject individually. This baseline is only defined for subjects that have been re-randomized by IXRS.

For certain datasets/analyses an '**intra-day baseline'** is derived (e.g., ECG, vital signs). This intra-day baseline is defined as the last non-missing assessment prior to study drug intake on the corresponding day. If there is no pre-dose assessment on the day (by time and date), then the intra-day baseline is considered to be missing. The intra-day baseline is calculated for parameters that are part of the hourly measurements on the day of first study drug intake (in TP1) and the day of first study drug intake of a re-initiated subject (in TP1).

For datasets where multiple measurements exist for the selection of the baseline assessment, the definition(s) is/are provided in the corresponding sections (e.g., spirometry or ECG data).

5.3 Treatment day

- The **'Treatment Day'** is defined as the day relative to the treatment start date in TP1, with the Treatment start date considered as 'Treatment Day 1', the day after the Treatment start date as 'Treatment Day 2' and so forth. There is no 'Treatment Day 0', so the day before the Start-of-Treatment date is 'Treatment Day –1'. The treatment day is derived for assessments in both TP1 and TP2.
- The **'Treatment day in TP1'** is derived as above, but only considering data in TP1.

- The **'Treatment day in TP2'** is derived based on the treatment start day in TP2 being 'Day 1', the day after treatment start being 'Day 2' and so forth. There is no 'Day 0' and no negative treatment day values. TP2 data will be assigned a 'Treatment day in TP2' only for subjects treated in TP2.

5.4 Analysis periods

5.4.1 Efficacy observation period

Efficacy observation periods are defined as:

- TP1: From treatment start date (TP1) to the date of last visit performed in TP1 (up to Month 6);
- TP2: From treatment start date (TP2) to the date of last visit performed in TP2 (up to Month 12). This period is defined for all re-randomized subjects;
- Pooled TP1/TP2: From treatment start date (TP1) to the date of last visit performed in TP1/TP2 (up to Month 12).

5.4.2 Safety observation period

As the observation period may differ according to endpoint, safety observation periods are defined along with the description of each analysis in the safety section.

5.4.3 Treatment groups for analysis according to treatment period

5.4.3.1 TP1

Any TP1 analyses will be summarized using the following 5 treatment groups:

- Cenerimod 0.5 mg
- Cenerimod 1 mg
- Cenerimod 2 mg
- Cenerimod 4 mg
- Placebo

5.4.3.2 TP2

Any TP2 analyses will be summarized using the following 2 treatment groups:

- Cenerimod 2 mg / Ex-4 mg
- Placebo / Ex-4 mg

Some TP2 analyses (as indicated in the respective sections) will also include the following treatment groups:

- Cenerimod 0.5 mg
- Cenerimod 1 mg

- Cenerimod 2 mg
- Placebo

5.4.3.3 TP1 and TP2 combined (and up to EOS)

Any analyses combining TP1 and TP2 data will be summarized using the following 6 treatment groups:

- Cenerimod 0.5 mg
- Cenerimod 1 mg
- Cenerimod 2 mg
- Cenerimod 2 mg / Ex-4 mg
- Placebo / Ex-4 mg
- Placebo

Outputs for CSR section 15.1, description of compliance and study treatment exposure during TP1+TP2, and outputs for CSR section 15.3 describing treatment-emergent data regardless of the time-period (e.g., Adverse Events, abnormalities) will also include the "Not re-randomized / Ex-4 mg" group.

5.4.3.4 Listings

Listings will be presented using the following treatment groups:

- Cenerimod 0.5 mg
- Cenerimod 1 mg
- Cenerimod 2 mg
- Cenerimod 2 mg / Ex-4 mg
- Placebo / Ex-4 mg
- Not re-randomized / Ex-4 mg
- Placebo

Listings presenting TP2 data only will use the following treatment groups:

- Cenerimod 2 mg / Ex-4 mg
- Placebo / Ex-4 mg

5.4.4 Visit windows

Data will be assigned into time windows for efficacy and safety analyses.

The windows are defined as shown in Table 4.

Table 4 Visit windows

Visit	Treatment day	First treatment day	Last treatment day
Baseline		–60	1
Month 1	30	2	45
Month 2	60	46	75
Month 3	90	76	105
Month 4	120	106	135
Month 5	150	136	165
Month 6	180	166	195
Month 7	210	196	225
Month 8	240	226	255
Month 9	270	256	285
Month 10	300	286	315
Month 11	330	316	345
Month 12	360	346	375

In the event that two visits are assigned to the same time window, choose the visit closest to the scheduled 'Treatment day', as displayed in Table 4. In the event that two visits are the same number of days from the scheduled 'Treatment day' select the first visit, with the exception that a regular visit will always be selected over an unscheduled visit.

5.5 Subgroups

The category in **bold type** is the reference category used for the analysis of subgroups.

The following subgroup variables are defined according to protocol:

- **Stratification variable:** Daily dose of OCS (**< 7.5 mg** or ≥ 7.5 mg prednisone equivalent) from IXRS system;
- **Stratification variable:** mSLEDAI-2K (**< 10** or ≥ 10) from IXRS system;
- Sex (**male**/female);
- Geographical region (**Europe**, US, Rest of World);
- Age (**< 65 years** vs ≥ 65 years) at Screening;
- Belimumab treatment status (**'treated'** vs 'not treated') at Screening;
- Race (**White**, American Indian or Alaska Native, Asian, and Black).

Both stratification variables are taken from the IXRS system; sex, age (< 65 years vs ≥ 65 years) and race are taken from the Demographics eCRF page. Region is derived based on the country of the sites. Belimumab treatment status is derived as a binary variable based on coding from the Previous/Concomitant Medication eCRF page.

5.6 Other derivations

The following conversion factors will be used to convert days into months or years: 1 month = 30.44 days, 1 year = 365.25 days. For time windows calculation, 1 month is expressed as 30 days.

6 STUDY SUBJECTS VARIABLES AND ANALYSES

6.1 Screen failures

6.1.1 Variables

Screen failures are defined as subjects, with a screen failure date in the database (Screening/Screen failure date present in the IXRS subject form), who are not randomized according to the eCRF Eligibility/Randomization form ("Was the subject randomized?" → 'No'), and who are not randomized according to the IXRS system (i.e., no randomization date/time and number in the IXRS 'Subject Form').

6.1.2 Analysis

The number of subjects screened, screening failures, subjects re-screened and re-screening failures, and reasons for screening failure will be summarized and listed using the SCR. Only reasons for the last screening attempt will be summarized. All reasons for screen failures will be included in the listing along with: date of Screening, screening attempt, an indicator variable ('Yes', 'No') for a successful or failed screening attempt, randomization date, number of days from successful Screening to Randomization and the verbatim reason for screen failure.

The same description will be provided for the screening failures related to COVID-19 pandemic.

6.2 Eligibility criteria

6.2.1 Variables

The inclusion and exclusion criteria information are taken from the Eligibility / Inclusion and Exclusion Criteria eCRF pages.

6.2.2 Analysis

All subjects with unmet eligibility criteria will be listed. Subjects randomized with unmet criteria will be flagged in the listing.

Eligibility criteria for screen failures not eligible as per inclusion/exclusion criteria will also be summarized. The table will only include screen failures not eligible as per inclusion/exclusion criteria.

In case a subject was screened multiple times with more than one screening failure, the last screening failure will be included in the summary. All screening attempts will be included in the listings.

6.3 Subject disposition

Subject disposition during TP1 includes the following variables, summarized by treatment group and overall using the FAS:

- Subjects randomized in TP1 (subjects with randomization date/time and number present in the IXRS 'Subject Form' for TP1).
- Subjects treated in TP1 (subjects with at least one dose of study treatment in the eCRF Study Treatment Log in TP1).
- Subjects who prematurely discontinued study treatment in TP1 (subjects with 'Discontinuation' as reason for treatment stop in the eCRF Study Treatment Log).
- Subjects who completed TP1 on-treatment (subjects without 'Discontinuation' as reason for treatment stop in the eCRF Study Treatment Log).
- Subjects who completed TP1 off-treatment.
- Subjects who prematurely discontinued study in TP1 (based on End of Study Status eCRF page with valid date and reason).
- Subjects taking part in the echocardiography ancillary study (subjects who were assigned to the echocardiography sub-study by IXRS).

Subject disposition during TP2 includes the following variables, summarized by treatment group (also including cenerimod 0.5 mg, 1 mg, 2 mg and placebo groups) and overall using the FAS-TP2:

- Subjects who were re-randomized in TP2 (subjects with randomization number present in IXRS for TP2).
- Subjects treated in TP2 (subjects with at least one dose of study treatment in the eCRF Study Treatment Log in TP2).
- Subjects who prematurely discontinued study treatment in TP2 (subjects with 'Discontinuation' as reason for treatment stop on the eCRF Study Treatment Log, occurring after start of TP2 treatment).
- Subjects who completed TP2 on-treatment (subjects without 'Discontinuation' as reason for treatment stop in the eCRF Study Treatment Log).
- Subjects who completed TP2 off-treatment.
- Subjects who prematurely discontinued study in TP2 (based on End of Study Status eCRF page with valid date and reason, occurring after start of TP2 treatment).

Subject disposition during TP1 and TP2 includes the following variables, summarized by treatment group and overall using the FAS:

- Subjects randomized in TP1.
- Subjects treated in TP1.
- Subjects re-randomized in TP2.
- Subjects treated in TP2.

- Subjects who prematurely discontinued treatment during TP1 or TP2 (subjects with 'Discontinuation' as reason for treatment stop in the eCRF Study Treatment Log).
- Subjects who prematurely discontinued study (based on End of Study Status eCRF page with valid date and reason).

The number of randomized subjects will also be summarized by country and site, using the SCR.

6.4 Study treatment discontinuation

6.4.1 Variables

Study treatment discontinuations are collected on the eCRF Study Treatment Log.

A premature permanent treatment discontinuation is defined as stopping treatment permanently prior to the scheduled Month 12 visit (Reason for treatment stop/dose change = 'Discontinuation'). Subjects discontinuing early are identified by having a discontinuation date on the corresponding eCRF page.

The primary reason for premature treatment discontinuation is selected from reasons listed in the eCRF.

Treatment discontinuation variables are also defined, by treatment period, for TP1 and TP2.

6.4.2 Analysis

The reasons for discontinuing treatment will be listed using the FAS and summarized as follows:

- During TP1: by treatment group and overall using the FAS.
- During TP2: by treatment group (also including cenerimod 0.5 mg, 1 mg, 2 mg and placebo groups) and overall using the FAS-TP2.
- During TP1 and TP2: by treatment group and overall using the FAS.

The same description will be provided for the treatment discontinuation related to COVID-19 pandemic.

In addition, the cumulative incidence of study treatment discontinuations during TP1 and TP2 by reason will be visualized.

6.5 Study discontinuation

6.5.1 Variables

A subject withdrawing from the study early is flagged 'No' for the question "Did the subject complete the study?" on the End of Study Status eCRF page, with a study withdrawal date entered. The primary reason for study withdrawal is selected from reasons listed in the eCRF.

Study discontinuation variables are also derived by period, for TP1 and TP2.

6.5.2 Analysis

The reasons for study discontinuation will be listed using the FAS and summarized as follows:

- During TP1: by treatment group and overall using the FAS.
- During TP2: by treatment group (also including cenerimod 0.5 mg, 1 mg, 2 mg and placebo groups) and overall using the FAS-TP2.
- During TP1, TP2 and follow-up period: by treatment group and overall using the FAS.

The same description will be provided for the study discontinuation related to COVID-19 pandemic.

In addition, the cumulative incidence of study discontinuation by reason will be visualized.

6.6 Protocol deviations

DVs will be summarized by DV category and subcategory by treatment group and overall. There will be separate tables for DVs during TP1 (using FAS), during TP2 (using FAS-TP2, including cenerimod 0.5 mg, 1 mg, 2 mg and placebo groups) and during the study (using FAS).

Important DVs will be summarized separately, in the same way.

The above summaries will be repeated for DVs and important DVs related to the COVID-19 pandemic.

A summary for DVs related to the conflict in Ukraine will be created.

DVs will be listed using the SCR. The listing will include a flag indicating whether a DV was related to the COVID-19 pandemic and whether a DV was related to the conflict in Ukraine.

A separate listing will present all subjects that were unblinded during the study including the event that triggered the unblinding request and the action taken following the unblinding using the FAS.

6.7 Inclusion/exclusion in analysis sets

6.7.1 Variables

The following variables are used for the analysis set outputs:

- Subjects in the FAS
- Subjects in the FAS-TP2
- Subjects in the PPS

- Subjects in the SAF
- Subjects in the SAF-TP2
- Subjects in the ECS
- Subjects in the PKS

Definitions of the analysis sets are presented in Section 4.1.

6.7.2 Analysis

The number and percentage of subjects in the FAS, FAS-TP2 and PPS will be summarized by treatment group and overall, using the FAS. The number and percentage of subjects in the SAF, SAF-TP2, ECS and PKS will be summarized by treatment group and overall, using the SAF.

Reasons for exclusion from any analysis set will be summarized and listed.

Reasons for excluding subjects from the PPS will be summarized in a table showing the following categories:

- Subject randomized but did not fulfill the entry criteria.
- Subject developed withdrawal criteria during the study, but did not withdraw.
- Incorrect treatment administration or any violation of treatment concept.
- Subjects who received forbidden concomitant medication/treatment.
- Key study procedures missed or performed out of time window.
- Other.

6.8 Subject characteristics

6.8.1 Demographics

6.8.1.1 Variables

The demographic variables are derived as follows:

- Sex;
- Age (years; continuous);
- Age group 1 (18–64, 65–75);
- Age group 2 (18–45, 46–64, 65–75);
- Weight (kg), by gender (female, male);
- Height (cm), by gender (female, male);
- BMI (kg/m^2; continuous);
- BMI (< 18.5, ≥ 18.5 – < 25.0, ≥ 25.0 – < 30.0, ≥ 30.0);

- Race (categorized as: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other);
- Ethnicity (categorized as: Hispanic or Latino, Not Hispanic or Latino, Unknown);
- Country;
- Region (Asia, Europe, Latin America, US, Rest of World);
- Childbearing potential (for female subjects only);
- Reason for not being of childbearing potential (for female subjects only);
- Smoking status (never smoked, current smoker, former smoker);

BMI is defined as: BMI = weight in kg / (height in m)^2.

Data are taken from the Demographics and Height and body weight (at Screening), Smoking/Alcohol eCRF pages. Region will be derived from the country of the site.

6.8.1.2 Analysis

Demographics will be summarized using descriptive statistics for continuous and categorical data using the FAS and PPS. Demographics will also be summarized by sex using the FAS.

Summary tables will be presented by treatment group and overall. A demographics listing will be produced using the SCR.

The percentages of women with childbearing potential will be based on number of female subjects in the study. The percentages of reasons for not being of childbearing potential will be based on the number of female subjects that have answered the eCRF question "Is the woman of childbearing potential?" with 'No'.

6.8.2 Stratification variables

6.8.2.1 Variables

OCS are collected on the Previous/Concomitant Medications eCRF page and are identified via coding. The stratification variable 'Dose of oral corticosteroids' is derived as a binary variable (< 7.5 mg/day vs ≥ 7.5 mg/day) at Randomization.

The mSLEDAI-2K data is collected on the mSLEDAI-2K eCRF page at Screening. mSLEDAI-2K is also derived as a binary variable (< 10 and ≥ 10).

The stratification variables, as entered by the investigator, are transferred by the IXRS provider.

6.8.2.2 Analysis

Number and percentage of subjects for each stratification factor separately as well as within each of the four strata will be summarized in shift tables according to eCRF as well as according to IXRS using the FAS.

6.8.3 Baseline disease characteristics

6.8.3.1 BILAG-2004 medical history

6.8.3.1.1 Variables

No variables are to be created, as data will only be listed.

6.8.3.1.2 Analysis

BILAG-2004 medical history will be listed using the SCR.

6.8.3.2 ACR classification criteria for SLE

6.8.3.2.1 Variables

The data are taken from the ACR Criteria eCRF specifications page. Binary variables are created for each of the categories listed on that eCRF page.

6.8.3.2.2 Analysis

ACR classification criteria will be summarized using descriptive statistics for categorical data using the FAS. Summary tables will be presented by treatment group and overall.

ACR classification criteria will be listed using the SCR.

6.8.3.3 mSLEDAI-2K at Screening

6.8.3.3.1 Variables

The mSLEDAI-2K relevant disease characteristics are recorded and derived from the data on the mSLEDAI-2K eCRF page at Visit 1 (Screening), and the variables include:

- Presence / no presence of each active descriptor
- Mucocutaneous score
- Musculoskeletal score
- Sum of the mucocutaneous and musculoskeletal score
- mSLEDAI-2K total score
- SLEDAI-2K total score
- mSLEDAI-2K total score as a category (≥ 10 and < 10)
- SLEDAI-2K total score as a category (≥ 10 and < 10)

mSLEDAI-2K

The SLEDAI-2K is a disease activity index of SLE based on the presence of 24 descriptors in 9 organ systems over the preceding 10 days.

Descriptors of the SLEDAI-2K are documented as either present or absent (or not done). Each of the descriptors is weighted and the total score of SLEDAI-2K is the sum of all

24 (weighted) descriptor scores. The range of the total SLEDAI-2K score is 0 to 105, with higher scores representing higher disease activity.

In this study, a modified SLEDAI-2K (mSLEDAI-2K) score is applied. The item related to leukopenia is excluded from the SLEDAI-2K scoring due to the mode of action of the compound (i.e., lymphocyte count reduction in peripheral blood). Therefore, the mSLEDAI-2K total score has only 23 descriptors and a maximum score of 104.

6.8.3.3.2 Analysis

The mSLEDAI-2K at Screening will be summarized using descriptive statistics for continuous and categorical data using the FAS.

Summary tables will be presented by treatment group and overall.

mSLEDAI-2K data will be listed using the SCR.

6.8.3.4 Physician's Global Assessment of disease

6.8.3.4.1 Variables

The PGA is taken from the Screening Physician's Global Assessment (PGA) eCRF page.

[redacted]

6.8.3.4.2 Analysis

PGA at Screening will be summarized using descriptive statistics for continuous and categorical data using the FAS.

Summary tables will be presented by treatment group and overall.

PGA data will be listed using the SCR.

6.8.3.5 British Isles Lupus Assessment Group

6.8.3.5.1 Variables

Data is taken from the derived BILAG-2004 screening summary eCRF page BILAG-2004 Grading. The data is received from an external vendor.

For each of the nine assessed BILAG-2004 categories gradings are displayed in 6 categories (A, B, C, D, E, not gradable).

6.8.3.5.2 Analysis

For each of the 9 subcategories descriptive summary statistics will be produced using the FAS, by treatment group and overall.

Data will also be listed using the SCR.

6.8.3.6 SELENA flare index

6.8.3.6.1 Variables

Data is taken from the SELENA Flare Index eCRF pages which are aggregated and provided by an external vendor.

Data are categorized into the following flare categories:

- No flare
- Mild or moderate flare
- Severe flare

6.8.3.6.2 Analysis

Flare data will be summarized using descriptive statistics using the FAS.

Summary tables will be presented by treatment group and overall.

Flare data will be listed using the SCR.

6.8.4 Other baseline characteristics

6.8.4.1 Discharge from medical monitoring on day of first study drug intake

Subjects fulfilling the discharge criteria at 6 hours on the day of first study drug intake may leave the hospital.

Subjects not fulfilling the discharge criteria at 6 hours will stay in hospital until the discharge criteria are fulfilled. The discharge criteria are checked every hour up to 12 hours. If the discharge criteria are not met after 12 hours, the subject will be permanently discontinued from study treatment.

Discharge information is taken from the eCRF pages “Discharge from Medical Monitoring - 6 hours” and “Discharge from Medical Monitoring - 12 hours”.

6.8.4.1.1 Variables

The number of subjects being discharged at 6 hours, between 6 and 12 hours and the number of subjects being discontinued after 12 hours of medical monitoring are derived on the day of first study drug intake.

For subjects that needed to stay longer than 6 hours, the time leaving the hospital is categorized hourly.

6.8.4.1.2 Analysis

The number of subjects being discharged at 6 hours, the number of subjects being discharged between 6 and 12 hours and the number of subjects being discontinued after 12 hours will be summarized descriptively using the SAF.

The number of subjects being discharged between 6 and 12 hours will be summarized hourly. For subjects not being discharged, reasons for not being discharged will be summarized in categories using the SAF.

Discharge data from the day of first study drug intake and the day of re-initiation will be listed using the SAF.

6.8.4.2 Other baseline characteristics

Other baseline characteristics collected during Screening include chest X-ray, contraceptive methods, physical examination, ophthalmological assessments, tuberculosis test, viral serology results and urinalysis. These are defined as collected on the eCRF and no derivation is required.

6.8.5 Medical history and current medical conditions

6.8.5.1 Variables - medical history and cardiovascular medical history / risk factors

6.8.5.1.1 Medical history (except SLE history, cardiovascular medical history and cardiovascular risk factors)

Medical history includes all diseases or diagnoses recorded on the Medical History (except SLE history, cardiovascular medical history and cardiovascular risk factors) eCRF page.

Reported terms are mapped to PTs using MedDRA at time of database closure.

The variables of interest are the PT and the primary SOC.

Current medical conditions are diseases and diagnoses that are ticked as ongoing at Screening and without an end date before or equal to the study treatment start date. In the event of a partial end date that overlaps with first dose (e.g., 'May 2019' and first dose occurred on '23 May 2019') or if an end date is missing, the medical condition is considered to be current if ongoing is ticked 'Yes'.

6.8.5.1.2 Cardiovascular medical history

Cardiovascular medical history is collected on the Cardiovascular Medical History eCRF page. The same definitions apply as defined for the medical history (except SLE history, cardiovascular medical history and cardiovascular risk factors).

6.8.5.1.3 Cardiovascular risk factors

Cardiovascular risk factors are collected on the Cardiovascular Risk Factors eCRF page. The same definitions apply as defined for the medical history (except SLE history, cardiovascular medical history and cardiovascular risk factors).

6.8.5.2 Analysis - medical history and cardiovascular medical history / risk factors

Medical history and cardiovascular medical history / risk factors will be summarized using the FAS.

Summaries will be presented by primary SOC and PT, sorted by descending frequency based on the total column. The MedDRA version used for reporting will be specified in the footnote of the applicable output.

Medical history data will be listed using the SCR.

6.8.6 Previous and concomitant therapies

6.8.6.1 Variables

Previous and concomitant therapies are collected on the Previous/Concomitant Medications eCRF page. Both non-SLE and SLE therapies are collected on this page. Previous and concomitant medications are categorized as follows:

- Previous non-SLE therapies.
- Study-concomitant non-SLE therapies.
- Study-concomitant non-SLE therapies at baseline.
- Previous SLE therapies.
- Study-concomitant (background) SLE therapies.
- Study-concomitant (background) SLE therapies at baseline.
- Previous cardiovascular therapies.
- Study-concomitant cardiovascular therapies.
- Study-concomitant cardiovascular therapies at baseline.

A previous therapy is any therapy for which the end date of therapy is prior to first study drug intake in TP1. A study-concomitant therapy is any therapy, that is either ongoing at the start of study treatment or is initiated between the start of the study treatment and the EOS visit. A study-concomitant therapy at baseline is any therapy, that either started on, or is ongoing at, the study treatment start date.

The reported names are coded using the WHO drug code dictionary and the ATC class according to the most current version at time of database closure. The variables of interest are the PT (standardized medication name) and the ATC code level 4.

The WHO drug version used for reporting is specified in the footnote of the applicable output.

6.8.6.1.1 Non-SLE therapies

A non-SLE therapy is any therapy collected on the Previous/Concomitant Medications eCRF page which is not a SLE therapy [see Section 6.8.6.1.2] and not a cardiovascular therapy [see Section 6.8.6.1.3].

6.8.6.1.2 SLE therapies

SLE therapies are identified based on the protocol-defined background SLE therapies [see protocol section 5.2.2, D-22.031] and a list based on WHODrug Global B3/C3-format is maintained in a separate document for their identification.

An SLE therapy is any therapy collected on the Previous/Concomitant Medications eCRF page which is included in the above-mentioned list and which is not a cardiovascular therapy [see Section 6.8.6.1.3]. All SLE therapies will also be classified into the categories mentioned in protocol section 5.2.2, using this list.

6.8.6.1.3 Cardiovascular therapies

A cardiovascular therapy is any therapy administered for cardiovascular conditions or risk factors, reported on the Previous/Concomitant Medications eCRF page as:

- Cardiovascular medical history.
- Cardiovascular risk factors.

6.8.6.1.4 Duration of medications/therapies

The duration of medication/therapy in years is defined as:

- Duration of medication/therapy (years) = therapy end date – therapy start date + 1 day / 365.25.

6.8.6.1.5 Data imputation

The purpose of imputing therapy dates is only to determine if a therapy is study-concomitant and/or study-concomitant at baseline.

Incomplete therapy end dates will be imputed with the latest date possible, e.g., if the day is missing, the last day of the respective month will be imputed, or if day and month are missing, the last day of the respective year will be imputed. End dates that are completely missing will not be imputed and the therapy is considered as ongoing.

If a therapy start date is completely missing, the earliest of study treatment start date or (imputed) therapy end date will be imputed.

Partial therapy start dates will be imputed as follows:

- Therapy start day missing: if the (imputed) therapy end date is on or after study treatment start date (or missing) and the partial therapy start date is in the same month and year as the study treatment start date, the study treatment start date is used. Otherwise, the first day of the month is used.
- Therapy start day and month missing: if the (imputed) therapy end date is on or after study treatment start date (or missing) and the partial therapy start date is in the same year as the study treatment start date, the study treatment start date is used. Otherwise, the first day of the year is used.

6.8.6.2 Analysis

Number (%) of subjects having taken at least one previous, study-concomitant or study-concomitant at baseline treatment will be summarized by ATC class and individual PT within each ATC class using the FAS, by treatment group and overall. For tables describing background SLE therapies, the category from protocol section 5.2.2 and identified in the file mentioned in Section 6.8.6.1.2 will be used instead of the ATC class.

In addition, a table summarizing changes in background SLE therapies during TP1 will be produced.

All previous and concomitant therapies will be listed using the SCR.

6.9 Study treatment exposure

6.9.1 Exposure to treatment

6.9.1.1 Variables

Duration of exposure (months) to study drug is defined as the time elapsing between the [date of first study drug intake and the date of last study drug intake + 1 (in days)] / 365.25 × 12, regardless of any treatment interruptions.

Duration of exposure is also derived by treatment period (TP1 and TP2).

Exposure to study drug is also derived in categories (≤ 3 months [91 days], > 3 months and ≤ 6 months [183 days], > 6 months and ≤ 9 months [274 days], > 9 months) for analyses of TP1 and TP2 combined and in monthly categories for analyses of TP1 and TP2 separately, using the variable 'Duration of exposure (months) to study drug'.

6.9.1.2 Analysis

The following summaries will be provided:

- Study treatment exposure during TP1 using the SAF.
- Study treatment exposure during TP1 by subgroup (sex, SLE age group, race) using the SAF.
- Study treatment exposure during TP2 using the SAF-TP2.
- Study treatment exposure during TP1 and TP2 using the SAF.

Exposure data will be listed using the SAF.

6.9.2 Compliance

6.9.2.1 Variables

Overall compliance (%) will be assessed through study treatment accountability using the following formula:

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

*The period is defined as the number of days during which study treatment should be taken as per actual visit dates.

If a subject did not return a kit, compliance will be set to missing for the respective period (e.g., between two visits). For the derivation of the overall compliance, the respective period will not be considered.

If a kit is replaced (e.g., because initial kit was lost by the subject), the initial kit will be ignored for the derivation of compliance.

The overall compliance will be categorized as:

- < 80%
- ≥ 80%

6.9.2.2 Analysis

Overall study compliance will be summarized using descriptive statistics by treatment group using the FAS. The "Not re-randomized / Ex-4 mg" group will also be displayed.

Compliance will also be summarized by period using the FAS for TP1 and the FAS-TP2 for TP2 (also including cenerimod 0.5 mg, 1 mg, 2 mg and placebo groups).

Compliance will be listed using the FAS.

6.10 Pharmacokinetic variables

PK plasma concentrations are collected 6 h after study drug administration on Day 1 (initiation or re-initiation) and pre-dose at Visits 3 (Month 1), 4 (Month 2), 5 (Month 3), 8 (Month 6), 14 (Month 12 or premature EOT), and at EOS.

To prevent unblinding, the results of the PK data are not communicated to the investigator, study personnel, subjects, Clinical Research Associates, or any sponsor or vendor/CRO personnel involved in the conduct of the study.

Results will be transferred by the bioanalytical laboratory for PK measurements to the sponsor and CRO personnel involved in the conduct of the study only after database lock.

6.10.1 Variables

Plasma concentrations are provided by the biomarker laboratory. Thus, no derivations are required.

6.10.2 Analysis

For PK variables quantitative descriptive statistics (including geometric mean and 95% CI) for plasma concentrations will be presented on the day of first study drug intake, the day of re-initiation and over time (Month 1, 2, 3, 6, 12, premature EOT, EOS), by visit and treatment group using the PKS.

The plasma concentration-time profiles of the values over time will be provided in figures (boxplot per treatment group and visit, from baseline to EOS) using the PKS.

A listing of PK data will be produced using the PKS.

7 EFFICACY VARIABLES AND ANALYSES

7.1 Overview

The primary efficacy variable of the study is the absolute change of the mSLEDAI-2K score from baseline to Month 6. Changes for all time points from Month 1 through Month 6 will be derived and included in the statistical analysis model of the primary endpoint.

There are two secondary endpoints that are analyzed in hierarchical manner for each dose level comparison following any rejections of dose level comparisons hypotheses of the primary endpoint:

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

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

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

The other efficacy endpoints are described as follows:

- Response at Month 6 on the mSLEDAI-2K score defined as a reduction from baseline of at least 4 points.
- Response (no worsening and improvement) at Month 6 on BILAG-2004 disease activity index defined as follows:

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

  and

  - Any BILAG A organ domain score at study baseline improved to B/C/D or any BILAG B organ domain score at study baseline improved to C/D.

- Response at Month 6 on SRI-5, -6, -7, -8 defined as the secondary endpoint (response at Month 6 on SRI-4) with reductions in mSLEDAI-2K of 5, 6, 7 and 8, instead of a reduction of 4.
- Occurrence of mild, moderate and severe flares from baseline up to Month 6.
- Time to first severe flare from baseline to Month 6 (severe flares defined as BILAG A organ domain score presence due to items that are new or worse).
- Time to first flare from baseline to Month 6.
- Change from baseline to Month 6 in PGA score.

Exploratory endpoints will be analyzed from baseline to a maximum of 12 months on all available assessments according to two groups:

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

Endpoints for Group 1:

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

Endpoints for Groups 1 and 2:

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

and

- Any BILAG A organ domain score at study baseline improved to B/C/D or any BILAG B organ domain score at study baseline improved to C/D.

- Response at each post-baseline assessment on SRI-4, -5, -6, -7, -8.
- Change from baseline to each post-baseline assessment in PGA score.
- Occurrence of flares and severe flares at each post-baseline assessment (defined as either 1 or more new BILAG A or 2 or more new BILAG B organ domain scores compared to the previous visit).
- Time to first severe flare from baseline to Month 12 (severe flares defined as BILAG A organ domain score presence due to items that are new or worse).
- Time to first flare from baseline to Month 12.

The PRO/QoL endpoints are defined as follows:

- Change from baseline to each post-baseline assessment in FACIT-Fatigue Scale score.
- Change from baseline to each post-baseline assessment in PGIS-F.
- PGIC-F score at each post-baseline assessment.
- Change from baseline to each post-baseline assessment in SF-36v2™.
- Change from baseline to each post-baseline assessment in the Lupus QoL questionnaire.

7.1.1 Overall testing strategy

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

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

<u>Change of mSLEDAI-2K from baseline to Month 6:</u>

- $H1_{mSLEDAI\text{-}2K}$: $cenerimod_{0.5\ mg}$ – placebo = 0
- $H2_{mSLEDAI\text{-}2K}$: $cenerimod_{1.0\ mg}$ – placebo = 0
- $H3_{mSLEDAI\text{-}2K}$: $cenerimod_{2.0\ mg}$ – placebo = 0
- $H4_{mSLEDAI\text{-}2K}$: $cenerimod_{4.0\ mg}$ – placebo = 0

The four alternative hypotheses are:

- $HA1_{mSLEDAI\text{-}2K}$: $cenerimod_{0.5\ mg}$ – placebo ≠ 0
- $HA2_{mSLEDAI\text{-}2K}$: $cenerimod_{1.0\ mg}$ – placebo ≠ 0
- $HA3_{mSLEDAI\text{-}2K}$: $cenerimod_{2.0\ mg}$ – placebo ≠ 0

- $HA4_{mSLEDAI-2K}$: $cenerimod_{4.0\ mg}$ – placebo ≠ 0

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

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

SRI-4

- $H1_{SRI-4}$: $cenerimod_{0.5\ mg}$/placebo = 1
- $H2_{SRI-4}$: $cenerimod_{1.0\ mg}$/placebo = 1
- $H3_{SRI-4}$: $cenerimod_{2.0\ mg}$/placebo = 1
- $H4_{SRI-4}$: $cenerimod_{4.0\ mg}$/placebo = 1

vs

- $HA1_{SRI-4}$: $cenerimod_{0.5\ mg}$/placebo ≠ 1
- $HA2_{SRI-4}$: $cenerimod_{1.0\ mg}$/placebo ≠ 1
- $HA3_{SRI-4}$: $cenerimod_{2.0\ mg}$/placebo ≠ 1
- $HA4_{SRI-4}$: $cenerimod_{4.0\ mg}$/placebo ≠ 1

and

BILAG-2004

- $H1_{BILAG}$: $cenerimod_{0.5\ mg}$/placebo = 1
- $H2_{BILAG}$: $cenerimod_{1.0\ mg}$/placebo = 1
- $H3_{BILAG}$: $cenerimod_{2.0\ mg}$/placebo = 1
- $H4_{BILAG}$: $cenerimod_{4.0\ mg}$/placebo = 1

vs

- $HA1_{BILAG}$: $cenerimod_{0.5\ mg}$/placebo ≠ 1
- $HA2_{BILAG}$: $cenerimod_{1.0\ mg}$/placebo ≠ 1
- $HA3_{BILAG}$: $cenerimod_{2.0\ mg}$/placebo ≠ 1
- $HA4_{BILAG}$: $cenerimod_{4.0\ mg}$/placebo ≠ 1

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

Each null hypothesis will be tested against the alternative hypothesis that the OR is different from 1 between cenerimod and placebo, at a given dose, in SRI-4 and BILAG-2004.

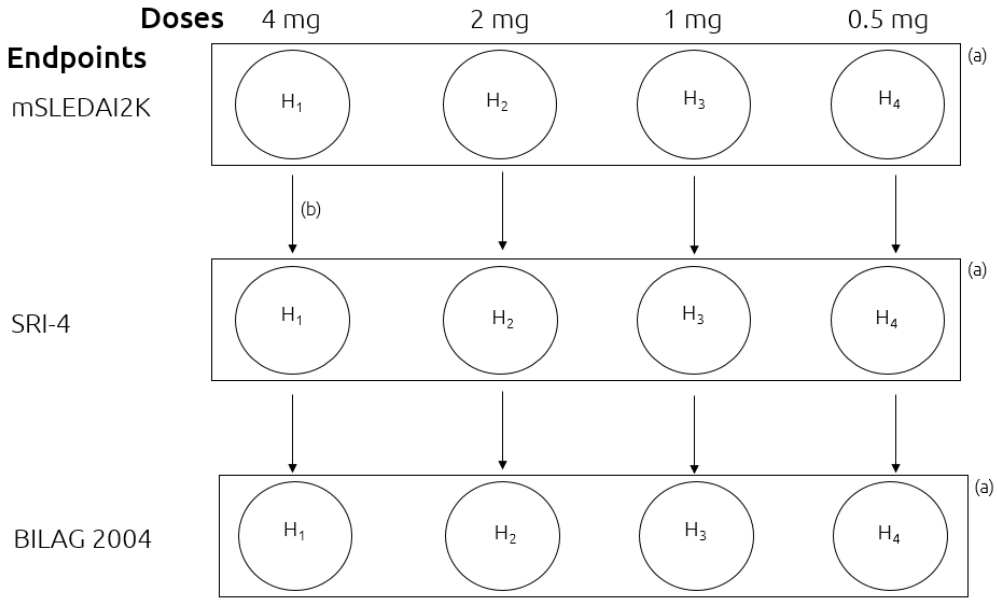
Within each primary and secondary endpoint analysis, the Hochberg procedure will be used to control the familywise error rate to ensure an overall two-sided Type I error rate of 5% for the four treatment group comparisons vs placebo. Further control of the study-wise error rate is conducted such that, for a given hypothesis to be rejected at a two-sided Type I error rate of 5%, the same dose-level hypothesis must have also been rejected for the previous endpoint(s), considering the above ordering of the endpoint hypotheses [see Figure 2].

This testing strategy protects the Type I error rate in the primary endpoint family with a slight increase in the Type I error rate in the secondary endpoint families.

Testing all four null hypotheses in the secondary endpoint families irrespective of which dose groups where significant in the previous endpoint family is the conservative approach (as opposed to only testing the significant doses from the previous endpoint family).

Claims for statistical significance will not be made on results from dose groups that have not been significant in a previous endpoint family. Such results are considered exploratory only.

Figure 2 Control of Type I error rate within each endpoint and treatment group



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

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

1

BILAG 2004 = British Isles Lupus Assessment Group-2004; mSLEDAI-2K = modified Systemic Lupus Erythematosus Disease Activity Index-2000; SRI = Systemic Lupus Erythematosus Responder Index.

7.2 Primary endpoint analysis

7.2.1 Overview of analyses

The main estimator as well as sensitivity and supplementary estimators for the primary estimand as defined in Section 3.1.1 are summarized in Table 5.

Table 5 Overview of analyses for primary estimand

Estimator	Section	Endpoint	Imputation method	Analysis
Main estimator	7.2.5	Change of mSLEDAI-2K from baseline to Month 6	None (MAR assumption)	Primary analysis (MMRM model) using the FAS. To ensure that the estimand based on the treatment policy strategy can be estimated, the value for the variable of change in mSLEDAI-2K is used regardless of occurrence of intercurrent events, such as treatment discontinuation.
Sensitivity estimator #1	7.2.6.1	Change of mSLEDAI-2K from baseline to Month 6	Multiple imputation under MAR	Simulation of 100 datasets based on MMRM model
Sensitivity estimator #2	7.2.6.2	Change of mSLEDAI-2K from baseline to Month 6	Multiple imputation under MNAR using copy reference	Simulation of 100 datasets based on MMRM model
Sensitivity estimator #3	7.2.6.3	Change of mSLEDAI-2K from baseline to Month 6	Multiple imputation under MNAR using jump to reference	Simulation of 100 datasets based on MMRM model
Sensitivity estimator #4	7.2.6.4	Change of mSLEDAI-2K from baseline to Month 6	None (MAR assumption)	Primary analysis (MMRM model) based on PPS
Sensitivity estimator #5	7.2.6.6	Change of mSLEDAI-2K from baseline to Month 6	None (MAR assumption)	Primary analysis (MMRM model) based on complete case analysis
Supplementary estimator #1 (dose response)	7.2.6.9	Dose response of mSLEDAI-2K from baseline to Month 6	None (MAR assumption)	
Supplementary estimator #2 (hypothetical estimand)	7.2.6.7	Change of mSLEDAI-2K from baseline to Month 6 (hypothetical estimand)	None (MAR assumption)	Primary analysis (MMRM model) for all on-treatment data. To ensure that the estimand based on the hypothetical strategy can be estimated, only values of mSLEDAI-2K prior to

Estimator	Section	Endpoint	Imputation method	Analysis
				occurrence of treatment discontinuation, the intercurrent event of interest, are used.
Supplementary estimator #3 (SLEDAI-2K)	7.2.6.8	Change of SLEDAI-2K from baseline to Months 1, 2, 3, 4, 5 and 6	None (MAR assumption)	Primary analysis (MMRM model)
Supplementary estimator #4 (subgroups)	7.2.7	Change of mSLEDAI-2K from baseline to Month 6	None (MAR assumption)	Subgroup analyses
Supplementary estimator #5 (response over time)	7.2.6.5	Change of mSLEDAI-2K from baseline to Months 1, 2, 3, 4, 5 and 6	None (MAR assumption)	Primary analysis (MMRM model)

FAS = Full Analysis Set; MAR = missing at random; MMRM = mixed model for repeated measures; MNAR= missing not at random; mSLEDAI-2K = modified Systemic Lupus Erythematosus Disease Activity Index-2000; PPS = Per-Protocol Set.

7.2.2 Variables

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

The null hypotheses for the primary endpoint will be tested using an MMRM on the change from baseline in mSLEDAI-2K for all available post-baseline scores from Months 1 to 6. This change is defined as the difference:

Change in mSLEDAI-2K = post-baseline mSLEDAI-2K score – baseline mSLEDAI-2K score.

Post-baseline visits will be assigned into time windows, as defined in Section 5.4.4, and the change from baseline will be computed based on the assigned visit labels.

Following the treatment policy estimand all data will be included in the analysis regardless of early treatment discontinuation or other intercurrent events.

The mSLEDAI-2K score is derived on the mSLEDAI-2K eCRF page for every visit and can be used without further derivation.

7.2.3 Handling of missing data

Based on the Phase 2 study, AC-064A201, it is expected that 6% of subjects will have a missing mSLEDAI-2K result at Month 6.

Missing data will not be imputed but will be handled by the MMRM assuming that the data are MAR.

Various sensitivity analyses will be performed to evaluate the robustness of this assumption [see Table 5].

A summary of the patterns of missingness from baseline up to Month 6 will be provided as well as a figure presenting the mean change from baseline in mSLEDAI-2K for study completers and withdrawals by reason.

7.2.4 Hypothesis, statistical model and assumptions

The hypotheses for the primary endpoint mSLEDAI-2K are presented in Section 7.1.1.

7.2.5 Main analysis

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

The null hypotheses for the primary endpoint will be tested using an MMRM on all available changes from baseline in mSLEDAI-2K for post-baseline scores from Months 1 through 6.

The following fixed effects will be included in the model:

- Treatment group.
- Month.
- Baseline mSLEDAI-2K score.
- Treatment group by month interaction.
- Baseline mSLEDAI-2K score by month interaction (as continuous variable).
- Stratification factor OCS (from IXRS).

The stratification factor mSLEDAI-2K at Screening will not be included in the model as the continuous baseline value is already included in the model.

A restricted maximum likelihood approach in combination with the Newton Raphson Algorithm will be used.

An unstructured (UN) covariance matrix will be used to account for the correlation between repeated measurements from the same subject. If this analysis fails to converge, the following structures will be tested in a subsequent order until model-convergence is achieved: heterogeneous Toeplitz (TOEPH); Toeplitz (TOEP); autoregressive (AR(1)); compound symmetry (CS). The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

The treatment effect for each cenerimod dose vs placebo will be estimated from the LSM differences for each dose vs placebo at Month 6 and their corresponding 95% CIs.

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

This analysis will be implemented using the following SAS® code:

```
proc mixed method=reml;
 class subjid ocs treatment month;
 model change = ocs sledai_bl treatment month treatment*month sledai_bl*month / ddfm=kr;
 repeated month / type = UN subject=subjid(treatment);

 slice treatment*month / sliceby=month pdiff cl;
run;
```

Efficacy data of the primary endpoint will be summarized descriptively and listed using the FAS.

7.2.6 Supplementary/sensitivity analyses

For all supplementary and sensitivity analyses of the primary endpoint analysis, the variable change from baseline in mSLEDAI-2K to Month 6 is derived as defined in Section 7.2.1 for the primary analysis.

7.2.6.1 Multiple imputation under MAR using mixed model for repeated measurements

This analysis will be conducted with multiple imputations in 3 steps using the FAS.

7.2.6.1.1 Step 1 (imputation)

Missing monthly mSLEDAI-2K scores will be imputed using a multiple imputation method [Rubin 1987], based on a model including the treatment group, the stratification factor OCS (from IXRS), the baseline mSLEDAI-2K score, and all post-baseline monthly scores up to Month 6.

Instead of imputing a single value for each missing observation, a set of values is generated from the model, resulting in as many distinct complete datasets without missing data.

More specifically, the imputations will be performed in two steps: ‘intermittent’ missing data (a monthly score is missing but one or more monthly score[s] is [are] available at following month[s]) will be first imputed by a Markov chain Monte Carlo method using a non-informative Jeffreys Prior, thus creating 100 partially imputed ‘monotone’ datasets, then the remaining missing data will be imputed once in each of these 100 ‘monotone’ imputed datasets using monotone regression leading finally to 100 complete imputed datasets. Imputed values will be restricted to remain in the clinically relevant range of [0, 104] but will not be rounded to integers.

The two-step multiple imputation procedure will be implemented by the following SAS® code:

```
proc mi data=h nimpute=100 seed=1234 minimum = . . 0 0 0 0 0 0 maximum = . . 104 104 104
104 104 104 minmaxiter=1000 out=h2;
  by trt;
  mcmc impute = monotone chain=single nbiter=200 niter=100;
  var ocs sledai_bl m1 -- m6;
run;

proc mi data=h2 nimpute=1 seed=1234 minimum = . . . 0 0 0 0 0 0 maximum = . . . 104 104 104
104 104 104 minmaxiter=1000 out=h3;
  by _imputation_;
  class treatment ocs;
  var treatment ocs sledai_bl m1 -- m6;
  monotone regression;
run;
```

In each imputed dataset, the change from baseline in mSLEDAI-2K from baseline to each monthly visit will be computed, as described for the primary endpoint. Imputed changes from baseline might not be integers.

7.2.6.1.2 Step 2 (analysis)

The analysis, within each imputed dataset, of the change in mSLEDAI-2K from baseline to Month 6 will be implemented by the following SAS® code:

```
proc mixed data=<data from step 1>;
class subjid ocs treatment month;
model change = ocs sledai_bl treatment month treatment*month sledai_bl*month / ddfm=kr;
repeated month / type = UN subject=subjid(treatment);

slice treatment*month / sliceby=month pdiff cl;
by _imputation_;
run;
```

7.2.6.1.3 Step 3 (combination)

Uncertainty in the imputations will be reflected appropriately in the analysis by combining the results on each imputed dataset into one summary measure. This method has been shown to be efficient in handling missing data if the missing data mechanism is missing completely at random or MAR [Schafer 1999].

The summary results across the 100 complete datasets will be aggregated following Rubin's rule. The final estimate is the mean of the 100 per-imputation estimates and the final variance is the sum of the average within-imputation variance and (1+1/100) times the between-imputation variance [Rubin 1987]. From the final point estimate and variance, the 95% CI will be determined. The corresponding p-value will be displayed.

The results aggregation as the final step of the multiple imputation procedure after analysis of the 100 complete datasets will be implemented by the following SAS® code:

```
proc mianalyze parms= <data from step 2 >;
 class treatment month;
 modeleffect treatment*month;
run;
```

The robustness of this model will be assessed via several sensitivity analyses as described in the following sections.

7.2.6.2 Multiple imputation under MNAR using copy reference

This sensitivity analysis will be performed using the FAS.

The analysis of the primary endpoint described in Section 7.2.6.1 is based on the MAR assumption that "missingness" is independent of missing responses conditionally on observed responses.

The observed data cannot be used to distinguish between MAR and MNAR missing data mechanisms [NRC Report 2010] and in incomplete-data settings a definitive MNAR analysis does not exist [Molenberghs 2004]. However, a selected number of MNAR models can be used to check the robustness of the results to departures from the MAR assumption.

An analysis based on a pattern-mixture model will be performed keeping a 'MAR imputation' in the placebo arm while using an 'MNAR approach' in the cenerimod arm. This pattern-mixture model will follow the multiple imputation procedure described in Section 7.2.6.1.1 but with a modification in the second imputation step (after imputation of the 'intermittent' missing data). The remaining missing data in subjects from the cenerimod arm will be imputed based on data from the placebo arm, assuming that subjects from the cenerimod arm who stop providing data will exhibit the same future trajectories as subjects in the placebo arm, while the remaining data in subjects from the placebo arm will be imputed under the MAR assumption [O'Kelly 2014]. This imputation model using the available post-baseline data of each cenerimod subject to be imputed is following the copy reference approach [Carpenter 2013].

Step 1 will be implemented by the following SAS® code:

```
proc mi data=h nimpute=100 seed=6789 minimum = . . . 0 0 0 0 0 0 maximum = . . . 104 104
104 104 104 104 minmaxiter=1000 out=h2;
mcmc impute = monotone;
var treatment ocs sledai_bl m1 -- m6;
run;

proc mi data=h2 nimpute=1 seed=6789 minimum = . . 0 0 0 0 0 0 maximum = . . 104 104 104 104
104 104 minmaxiter=1000 out=h3;
by  imputation ;
class treatment ocs;
var ocs sledai_bl m1 -- m6;
mnar model (m1 -- m6 / modelobs=(treatment="placebo"));
monotone regression;
run;
```

Steps 2 and 3 will be implemented as in Section 7.2.6.1.2 and 7.2.6.1.3.

7.2.6.3 Multiple imputation under MNAR using jump to reference

This sensitivity analysis will be performed using the FAS.

Steps 1 to 3 are repeated as described for the copy reference model in Section 7.2.6.2, with a code change in step 1, as displayed below. The jump to reference model is implemented by missing value imputations, separately for every visit, i.e., the imputation procedure will be repeated 6 times, once for each of the monthly visits.

```
proc mi data=h nimpute=100 seed=123 minimum = . . 0 0 0 0 0 0 maximum = . . 104 104 104 104
104 104 minmaxiter=1000 out=h2;
mcmc impute = monotone;
var ocs sledai_bl m1 -- m6;
run;

proc mi data=h2 nimpute=1 seed=123 minimum = . . 0 maximum = . . 104 minmaxiter=1000 out=m1;
by _imputation_;
class treatment ocs;
var ocs sledai_bl m1;
mnar model (m1 / modelobs=(treatment="placebo"));
monotone regression;
run;

proc mi data=m1 nimpute=1 seed=123 minimum = . . 0 maximum = . . 104 minmaxiter=1000 out=m2;
by _imputation_;
class treatment ocs;
var ocs sledai bl m2;
mnar model (m2 / modelobs=(treatment="placebo"));
monotone regression;
run;

…

proc mi data=m5 nimpute=1 seed=123 minimum = . . 0 maximum = . . 104 minmaxiter=1000 out=m6;
by _imputation_;
class ocs;
var ocs sledai_bl m6;
mnar model (m6 / modelobs=(treatment="placebo"));
monotone regression;
run;
```

7.2.6.4 Analyses based on PPS

The analysis of the primary endpoint as described in Section 7.2.5 will be conducted using the PPS.

7.2.6.5 Treatment effect over time

All monthly estimates related to the primary endpoint variable from the primary analysis model described in Section 7.2.5 will be reported as well.

Figures presenting the LSM differences versus placebo and their 95% CIs over time will be produced by treatment group using the FAS.

7.2.6.6 Complete case analysis

Only data from subjects with the complete information available at all visits from baseline to Month 6 will be included in the analysis of the primary endpoint as described in Section 7.2.5 (based on the FAS).

7.2.6.7 Hypothetical estimand analysis

This supplementary analysis does not use the treatment policy strategy to account for treatment discontinuation that is used for the primary analysis estimand, but rather, the hypothetical strategy. This means that all assessments collected after premature treatment discontinuation are not included in the analysis.

The analysis will be conducted in the same way as the primary analysis as described in Section 7.2.5 (based on the FAS).

7.2.6.8 Analyses based on SLEDAI-2K

7.2.6.8.1 Variable

The derivation of the 'full' SLEDAI-2K is based on the derived mSLEDAI-2K scores of the primary endpoint [see Section 7.2.1], including baseline and Month 1 to Month 6 scores, and the leukocyte value (from the central laboratory) at the corresponding visit.

If leukopenia is present at the corresponding visit the SLEDAI-2K score derives as:

SLEDAI-2K at Visit X = mSLEDAI-2K at Visit X + 1.

If leukopenia is not present or the leukocyte data are missing at the corresponding visit the SLEDAI-2K score is derived as:

SLEDAI-2K at Visit X = mSLEDAI-2K at Visit X.

Leukopenia is defined as a leukocyte value of $< 3000 \times 10^9$/L (per visit).

7.2.6.8.2 Analysis

The analysis of the primary endpoint as described in Section 7.2.5 will be conducted on the SLEDAI-2K.

7.2.6.9 Dose-response analysis

7.2.6.9.1 Dose-response analysis

The objective of this supplementary analysis is to assess overall dose-response using modeling and multiple comparison procedures on the primary efficacy endpoint (change in mSLEDAI-2K from baseline to Month 6).

7.2.6.9.2 Hypothesis and model

The null hypothesis is that there is no dose response for the primary efficacy endpoint from baseline to Month 6, and the alternative hypothesis is the existence of a dose response:

$H_0: p_d \geq p_{Placebo}$ for all doses d = 0.5, 1, 2, 4 mg

vs

$H_1: p_d < p_{Placebo}$ for at least 1 dose d =0.5, 1.0, 2.0, 4.0 mg

To meet the objective of defining a dose response on the reduction of mSLEDAI-2K from baseline to Month 6, the null hypotheses must be rejected with an exploratory one-sided significance level of 5%.

Dose-response data are analyzed using the MCP-Mod approach [Bretz 2005]. In brief, this methodology consists of three steps:

1. MCP step to establish a dose-response signal (i.e., the dose-response curve is not flat).
2. Mod step: Selecting the best dose-response model for the observed data out of a pre-specified set of candidate models, and
3. Mod step: Estimating target dose(s) of interest via modeling.

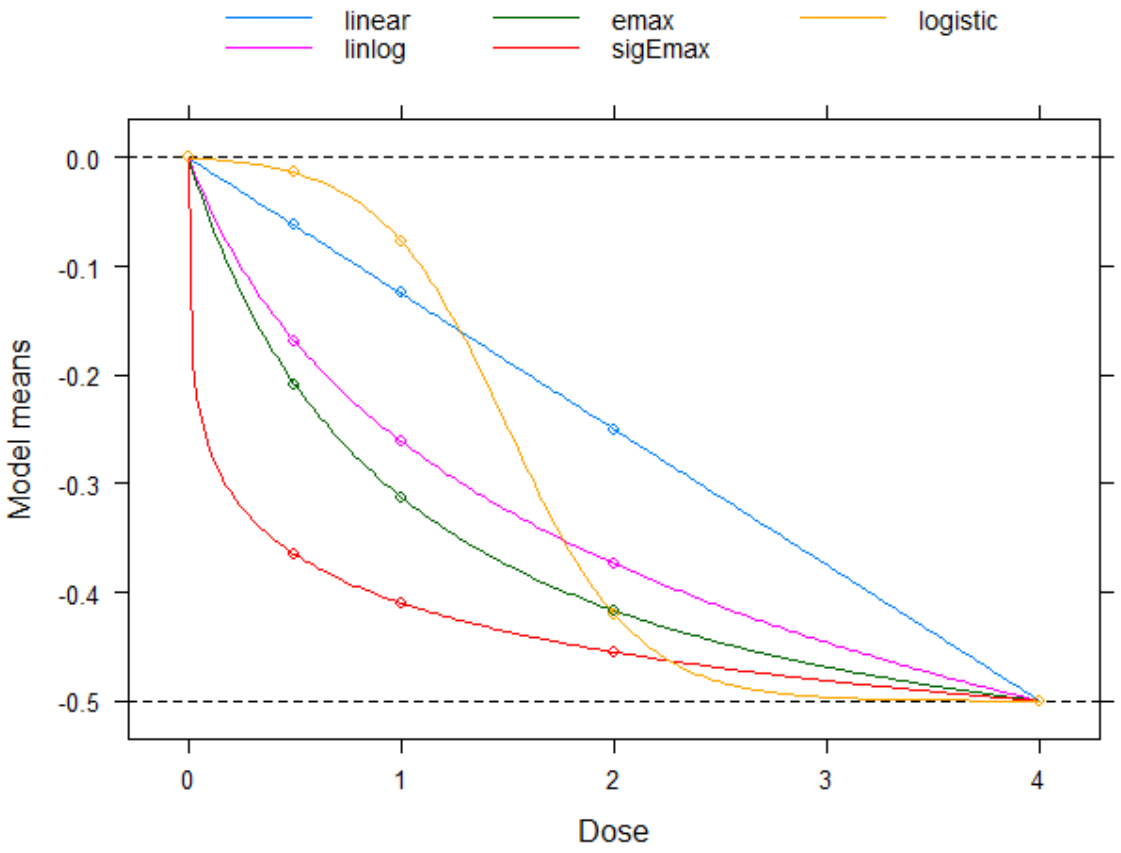
Five candidate models are considered: linear, linlog, E_{max}, sigmoidal E_{max} and logistic. See Table 6 for the parameterization of the dose-response models and Figure 3 as an illustration of their basic shapes. The initial values for the parameters are needed in the MCP step of the procedure. They will be estimated in the Mod step based on the actual data.

Table 6 Parameterization of models considered in MCP-Mod analyses

Model	**Response***	**Initial value(s) for parameters**
Linear	$E_0 + \text{delta} \bullet dose$	NA*
Linear in log	$E_0 + \text{delta} \bullet \log(dose + 0.5)$	NA*
E_{max}	$E_0 + E_{max} \bullet dose/(ED_{50} + dose)$	$ED_{50} = 1$
Sigmoidal E_{max}	$E_0 + E_{max} \bullet dose^h/(ED_{50}^h + dose^h)$	$ED_{50} = 1.5$, h = 0.3
Logistic	$E_0 + E_{max}/(1 + \exp[\{ED_{50} - dose\}/\text{delta}])$	$ED_{50} = 1.5$, delta = 0.3

Dose = 0, 0.5, 1, 2 and 4 mg of cenerimod;
*Not applicable for E0, delta (in linear and linlog models), and E_{max}
ED_{50} = dose giving half of the asymptotic maximum effect; E_{max} = maximum effect; linlog = linear in log; MCP-Mod = multiple comparison procedures - modeling; NA = not applicable.

Figure 3 Dose-response curves considered in MCP-Mod procedure



E_{max} = maximum effect; linlog = linear in log; MCP-Mod = multiple comparison procedures - modeling.

Note that the 'Model means' on the vertical axis are plotted on a scale from 0 to –0.5 for illustrative purposes. The actual scale will depend on the endpoint analyzed.

The null hypothesis of 'no dose response' will be rejected if at least one of the five multiple contrast tests has a multiplicity adjusted p-value < 0.05.

All statistically significant models (i.e., with a multiplicity adjusted p-value < 0.05) will be fitted in the Mod step and for each model AIC will be calculated. The smaller the value of AIC (= model deviance + 2 times the number of model parameters), the better the fit. The analysis will be performed using the R *DoseFinding* package [Bornkamp 2016].

7.2.6.9.3 Handling of missing data

Missing data will not be imputed but will be handled by the underlying MMRM model assuming that the data are MAR.

7.2.6.9.4 Variables

The LSM estimates of the change from baseline to Month 6 of all treatment groups and placebo are taken from the model of the primary efficacy endpoint. In addition, the variance/covariance matrix of the LSM estimates at Month 6 is output by SAS®. Both the LSM estimates, and the variance/covariance matrix are transferred into and analyzed using the R *DoseFinding* package.

7.2.6.9.5 Analysis

The analysis will be based on the R-code '*Mods'* and *'MMfit'*.

In the '*Mods* function call' the candidate models are specified, together with the assumed placebo and maximum effects. In the call to the *MCPMod* function,

- *doses* is a vector of length 5, corresponding to Planned Dose for TP1 (increasing order),
- *est* is a vector of length 5, corresponding to the LSM estimates of the change from baseline to Month 6 of all treatment groups and placebo (sorted by dose),
- *C* is the variance/covariance matrix (of dimensions 5 × 5) of the LSM estimates at Month 6 (sorted by dose),
- *Delta* is a target difference vs. placebo [see protocol section 10.5, D-22.031].

The object *MMfit* is summarized to obtain the MCP test, parameter estimates, target dose and AIC. These elements will be summarized. The object will be plotted to display the fitted dose-response curves.

The selected model will be fitted using the *fitMod* function and plotted together with the LSM estimates and confidence intervals from the primary analysis.

```
doses <- c(0,0.5,1,2,4)

# define candidate models
mods2 <- Mods(linear = NULL, linlog = NULL, emax = 1, sigEmax = c(1.5, 0.3), logistic =
c(1.5, 0.3), doses = doses, direction="decreasing")

# MCPMod
MMfit  <-  DoseFinding::MCPMod(type="general",  dose=doses,  resp=est,  S=as.matrix(C),
models=mods2, alpha=0.05, selModel="AIC", Delta=1.5)

# fit the selected model
MMsel <- fitMod(type="general", dose=doses, resp=est, S=as.matrix(C), model=MMfit$selMod)

# extract predicted values to plot, together with CI
pred <- predict (MMsel, se.fit=TRUE, doseSeq=seq(0,4,0.05),predType="ls-means")
pred$LB <- pred$fit - qnorm(0.975)*pred$se.fit
pred$UB <- pred$fit + qnorm(0.975)*pred$se.fit
```

7.2.7 Subgroup analyses

The aim of these exploratory subgroup analyses, classifying subjects according to important baseline characteristics, is to explore the consistency of treatment effect in a variety of relevant subject subgroups to support the efficacy evaluation of cenerimod in this indication.

7.2.7.1 Variables

Subgroup variables are defined as in Section 5.5.

7.2.7.2 Analysis

The same model as for the main analysis described in Section 7.2.5 will be fitted per subgroup. Stratification factor OCS will not be included as a fixed effect in the model for subgroup analysis by daily dose of OCS.

Summary tables will be produced, similar to those produced for the primary efficacy analysis, by subgroup.

Forest plots will be produced, displaying the LSM differences for each dose vs placebo including 95% CIs at Month 6. The forest plot will include an 'overall' treatment effect, based on the primary efficacy analysis and a reference line for the zero effect.

7.3 Secondary endpoints analysis

7.3.1 Response at Month 6 on SRI-4

The composite endpoint (SRI-4 response at Month 6) is a binary endpoint based on three variables, as defined below.

The mSLEDAI-2K score is derived on the mSLEDAI-2K eCRF page for every visit and can be used without further derivation. The PGA data is taken from the Physician's Global Assessment (PGA) eCRF page.

A time windowing approach, as defined in Section 5.4.4, is applied for the variable derivation.

7.3.1.1 Overview of analyses

The main estimator as well as sensitivity and supplementary estimators for the secondary estimand #1 as defined in Section 3.1.1 are summarized in Table 7.

Table 7 Overview of analyses for secondary estimand #1

Estimator	Section	Endpoint	Imputation method	Analysis
Main estimator	7.3.1.5	Response on SRI-4 at Month 6	None (MAR assumption)	Repeated measurements GLMM. To ensure that the estimand based on the treatment policy strategy can be estimated, the value for the variable of SRI-4 is used regardless of occurrence of intercurrent events, such as treatment discontinuation.
Sensitivity estimator #1	7.3.1.6.1	Response on SRI-4 at Month 6	None (MAR assumption)	Repeated measurements GLMM based on PPS.
Sensitivity estimator #2	7.3.1.6.2	Response on SRI-4 at Month 6	MI assuming MAR	Repeated measurements GLMM on complete data imputed using MI assuming MAR.
Sensitivity estimator #3	7.3.1.6.3	Response on SRI-4 at Month 6	MI assuming MNAR (tipping point)	Repeated measurements GLMM on complete data imputed using MI assuming MNAR.
Supplementary estimator #1 (response over time)	7.3.1.6.4	Response on SRI-4 at Month 1, 2, 3, 4, 5 and 6	None (MAR assumption)	Repeated measurements GLMM.
Supplementary estimator #2 (subgroups)	7.3.1.7	Response on SRI-4 at Month 6	None (MAR assumption)	Subgroup analyses.

GLMM = generalized linear mixed model; MAR = missing at random; MI = multiple imputation; PPS = Per-Protocol Set; SRI = Systemic Lupus Erythematosus Responder Index.

7.3.1.2 Variables

The three variables are defined as follows:

mSLEDAI-2K Responder

The absolute change of the mSLEDAI-2K from baseline to Month 6 (using time window approach) is defined as:

Change in mSLEDAI-2K = mSLEDAI-2K score at Month 6 – mSLEDAI-2K score at baseline.

Subjects with a reduction from baseline to Month 6 of ≥ 4 are considered to be responders (Responder = 1), subjects with a reduction of < 4 or an increase are considered to be non-responders (Responder = 0).

BILAG-2004 Responder

A responder (1) is defined as having no new BILAG A organ domain score and at most one new BILAG B organ domain score assessed for the nine body systems. A responder can only be assessed if the full information of all body systems is available.

Non-responders (0) are defined as having one or more new BILAG A organ domain scores or at least two or more BILAG B organ domain scores. In the event of incomplete data in at least one of the body systems, but sufficient information to fulfill the non-response criteria, the subject will be considered to be a non-responder.

Subjects that fit none of the above criteria will be assigned a missing value.

PGA Responder

The absolute change of PGA from baseline to Month 6 is defined as follows:

Change of PGA = PGA value at Month 6 – PGA value at baseline.

A responder (1) is a subject with an increase of ≤ 0.3 compared to baseline. A non-responder (0) is defined as having an increase of > 0.3 compared to baseline. Subjects with missing data either at baseline or Month 6 will be assigned a missing value.

Composite endpoint

A responder (1) for the endpoint SRI-4 response at Month 6 is defined as a responder of all three variables, as defined above. If at least one of the three variables indicate non-response, the subject is considered to be a non-responder (0). If at least one of the three variables is missing, the subject is assigned a missing value, unless at least one non-missing variables indicates non-response.

Data of this endpoint is derived for all monthly post-baseline visits up to Month 6.

7.3.1.3 Handling of missing data

Missing data will not be imputed but will be handled by the repeated measurements GLMM, assuming that the data are MAR.

A summary of the patterns of missingness from baseline up to Month 6 will be provided.

7.3.1.4 Hypothesis, statistical model and assumptions

The hypotheses for the secondary endpoint (response at Month 6 based on SRI-4) are presented in Section 7.1.1.

7.3.1.5 Analysis

This secondary endpoint will be analyzed using the FAS. Following the treatment policy estimand all data will be included in the analysis regardless of early treatment discontinuation or other intercurrent events.

A repeated measurements GLMM with the logit link function will be fitted with the secondary endpoint SRI-4 as dependent variable (from Month 1 to Month 6). The model will include the treatment group, month, the treatment group by month interaction, and the OCS and mSLEDAI-2K stratification variables (from IXRS) as fixed effects.

An unstructured (UN) covariance structure will be used for estimation of the correlation between responses measured within the same subjects across multiple months. If this analysis fails to converge, the following structures will be tested in a subsequent order until model-convergence is achieved: heterogeneous Toeplitz (TOEPH); Toeplitz (TOEP); autoregressive (AR(1)); compound symmetry (CS).

Parameters will be estimated using restricted pseudo-likelihood with Newton Raphson ridging optimization and the Kenward-Roger method for calculating the denominator degrees of freedom.

The study treatment groups will be compared against placebo at each month using ORs and 95% CIs. The main comparisons are at Month 6.

The analysis will be implemented by the following SAS® code:

```
proc glimmix;
  nloptions technique=nrridg;
  class subjid ocs sledai_sc treatment month;
  model response = ocs sledai_sc treatment month treatment*month / link=logit dist=bin
ddfm=kr;
  random month / type=un subject=subjid rside;
  lsmeans treatment*month / ilink cl; /* estimates event rates */
  lsmeans treatment*month / oddsratio diff cl; /* estimates ORs */
run;
```

Data for this endpoint will be summarized descriptively and listed using the FAS.

7.3.1.6 Supplementary/sensitivity analyses

7.3.1.6.1 Analyses based on PPS

The analysis of the secondary endpoint will be repeated using the PPS.

7.3.1.6.2 Multiple imputation under MAR

7.3.1.6.2.1 Step 1 (imputation)

Missing monthly SRI-4 scores will be imputed using a multiple imputation method [Rubin 1987], based on a model including the treatment group, the stratification factors OCS and mSLEDAI-2K (from IXRS), and all post-baseline monthly scores up to Month 6.

Instead of imputing a single value for each missing observation, a set of values is generated from the model, resulting in as many distinct complete datasets without missing data.

More specifically, the imputations will be performed in two steps: first, 'intermittent' missing data (a score is missing but one or more score[s] is [are] available at following month[s]) will be first imputed by a MCMC method using a non-informative Jeffreys Prior, thus creating 100 partially imputed 'monotone' datasets.

MCMC assumes multivariate normality for the SRI-4 scores at subsequent visits. This assumption is not satisfied for this binary endpoint. However, if the proportion of non-monotone data is not large, this will have a limited impact on the overall results. The values imputed by the MCMC will be rounded using adaptive rounding [Bernaards 2007]. In adaptive rounding, instead of using a fixed threshold of 0.5, the threshold is based on the imputed data using a normal approximation for a binomial distribution. This threshold is defined as follows, where μ is the mean of the imputed variable (including available binary observations and imputed continuous values) computed using unrounded values and Φ^{-1} (μ) is the z value from a standard normal distribution (inverse of the standard normal cumulative distribution):

$$threshold = \mu - \Phi^{-1}(\mu)\sqrt{\mu(1-\mu)}$$

Values greater or equal to the threshold are rounded to 1, and values smaller than the threshold are rounded to 0.

In the second step, the remaining missing data will be imputed once in each of these 100 'monotone' imputed datasets using logistic regression leading finally to 100 complete imputed datasets.

The multiple imputation procedure will be implemented by the following SAS® code:

```
proc mi data=h nimpute=100 seed=12345 out=h2;
  by treatment;
  mcmc impute = monotone chain=single nbiter=200 niter=100;
  var ocs sledai m1 -- m6;
run;

< Round imputed values in h2, using adaptive rounding >

proc mi data=h2 nimpute=1 seed=12345 out=h3;
  by_imputation_;
  class treatment ocs sledai m1 -- m6;
  var treatment ocs sledai m1 -- m6;
  monotone logistic;
run;
```

7.3.1.6.2.2 Step 2 (analysis)

Each imputed dataset will be analyzed using the same model as for the main analysis of SRI-4 described in Section 7.3.1.5.

7.3.1.6.2.3 Step 3 (combination)

Uncertainty in the imputations will be reflected appropriately in the analysis by combining the results on each imputed dataset into one summary measure. This method has been shown to be efficient in handling missing data if the missing data mechanism is missing completely at random or MAR [Schafer 1999].

The summary results across the 100 complete datasets will be aggregated following Rubin's rule. The final estimate is the mean of the 100 per-imputation estimates and the final variance is the sum of the average within-imputation variance and (1+1/100) times the between-imputation variance [Rubin 1987]. From the final point estimate and variance, the 95% CI will be determined. The corresponding p-value will be displayed.

The results aggregation as the final step of the multiple imputation procedure after analysis of the 100 complete datasets will be implemented by the following SAS® code:

```
proc mianalyze parms(classvar=classval)=<data from step 2 >;
  class treatment month;
  modeleffect treatment*month;
  ods output parameterestimates=<result dataset>;
run;
```

7.3.1.6.3 Tipping point analysis

This analysis will be implemented in three steps as described in Section 7.3.1.6.2.

The difference here is that, at the end of step 1, a "non-responder" status is imposed at Month 6 on withdrawals with an extra probability above that is modeled by the MAR assumption in the active treatment groups. Imputations under MAR in the placebo arm are not changed. This is implemented using the following example SAS® code:

```
data h4;
  set h3;
  * delta represents a probability of resetting imputed responder status to non-responder;
  delta = 0.05;
  call streaminit(1234);
  if m6_miss = "Y" and trt ne "Placebo" then do; * if responder status was missing (i.e.,
imputed) and treatment group is not placebo;
    if rand("Uniform") < delta then m6 = 0;
  end;
run;
```

For example, if this probability is set to 10%, for every 10 subjects imputed as responders in the active treatment groups under the MAR assumption, 1 subject is randomly re-imputed as a non-responder. Note, that some subjects are of course imputed as non-responders directly under MAR.

To stress test the result from the main analysis, we impose a succession of probability adjustments starting at 5%, incrementing by 5% up to 100%.

7.3.1.6.4 Treatment effect over time

7.3.1.6.4.1 Variables

To assess the treatment effect over time on SRI-4, the composite endpoint SRI-4 response will be calculated as described in Section 7.3.1.2 for all post-baseline visits from Months 1 to 6.

7.3.1.6.4.2 Analysis

The analysis will be performed based on the same repeated measurements model as described in Section 7.3.1.5.

A figure presenting OR (95% CI) vs placebo over time will be produced.

7.3.1.7 Subgroup analyses

The same model as for the main analysis described in Section 7.3.1.5 will be fitted per subgroup.

A forest plot will be produced, displaying the OR for each dose vs placebo including 95% CIs at Month 6. The forest plot will include an 'overall' treatment effect, based on the secondary efficacy analysis and a reference line for no treatment effect at OR = 1.

For the analyses of the OCS and mSLEDAI-2K subgroups, the corresponding subgroup will not be included as a stratification factor in the model.

7.3.2 Response (no worsening) at Month 6 on BILAG-2004 disease activity index

7.3.2.1 Overview of analyses

The main estimator as well as sensitivity and supplementary estimators for the secondary estimand #2 as defined in Section 3.1.1 are summarized in Table 8.

Table 8 Overview of analyses for secondary estimand #2

Estimator	Section	Endpoint	Imputation method	Analysis
Main estimator	7.3.2.5	Response on BILAG-2004 at Month 6	None (MAR assumption)	Repeated measurements GLMM. To ensure that the estimand based on the treatment policy strategy can be estimated, the value for the variable of BILAG-2004 is used regardless of occurrence of intercurrent events, such as treatment discontinuation.
Sensitivity estimator #1	7.3.2.6.1	Response on BILAG-2004 at Month 6	None (MAR assumption)	Repeated measurements GLMM based on PPS
Sensitivity estimator #2	7.3.2.6.2	Response on BILAG-2004 at Month 6	MI assuming MAR	Repeated measurements GLMM on complete data imputed using MI assuming MAR
Sensitivity estimator #3	7.3.2.6.3	Response on BILAG-2004 at Month 6	MI assuming MNAR (tipping point)	Repeated measurements GLMM on complete data imputed using MI assuming MNAR
Supplementary estimator #1 (response over time)	7.3.2.6.4	Response on BILAG-2004 at Month 1, 2, 3, 4, 5 and 6	None (MAR assumption)	Repeated measurements GLMM.
Supplementary estimator #2 (subgroups)	7.3.2.7	Response on BILAG-2004 at Month 6	None (MAR assumption)	Subgroup analyses

BILAG-2004 = British Isles Lupus Assessment Group-2004; GLMM = generalized linear mixed model; MAR = missing at random; MI = multiple imputation; PPS = Per-Protocol Set.

7.3.2.2 Variables

The binary response variable of this endpoint is derived as described in Section 7.3.1.2 for the BILAG-2004 endpoint.

7.3.2.3 Handling of missing data

Missing data will not be imputed but will be handled by the repeated measurement's GLMM assuming that the data are MAR.

A summary table of the patterns of missingness from baseline up to Month 6 will be provided.

7.3.2.4 Hypothesis, statistical model and assumptions

The hypotheses for the secondary endpoint (response at Month 6 based on BILAG-2004) are presented in Section 7.1.1.

7.3.2.5 Analysis

The analysis will be performed based on the same repeated measurements model as described in Section 7.3.1.5.

Data of this endpoint will be summarized descriptively and listed using the FAS.

7.3.2.6 Supplementary/sensitivity analyses

7.3.2.6.1 Analyses based on PPS

The analysis of the secondary endpoint will be repeated using the PPS.

7.3.2.6.2 Multiple imputation under MAR

This analysis will be implemented as described in Section 7.3.1.6.2.

7.3.2.6.3 Tipping point analysis

This analysis will be implemented as described in Section 7.3.1.6.3.

7.3.2.6.4 Treatment effect over time

7.3.2.6.4.1 Variables

The same variable definitions as for the secondary endpoint are used. No imputation methods are applied. The endpoint is also derived for the time points Month 1 to Month 5.

7.3.2.6.4.2 Analysis

The repeated measurements analysis will be conducted in the same way as for the secondary endpoint described in Section 7.3.1.5.

A figure presenting OR (95% CI) vs placebo over time will be produced.

7.3.2.7 Subgroup analyses

Subgroup analyses will be conducted in the same way as defined for the secondary endpoint SRI-4.

7.4 Other efficacy endpoints analysis

No imputation methods are applied for the other efficacy endpoints. All other efficacy endpoints will be summarized descriptively and listed using the FAS. Additional analyses for the other efficacy endpoints are described in the sections below.

The time window approach, as defined in Section 5.4.4, is applied for the derivation of the following variables.

7.4.1 Response at Month 6 on the mSLEDAI-2K score

7.4.1.1 Variables

The binary response variable of this endpoint is derived as described in Section 7.3.1.2 for the mSLEDAI-2K endpoint.

7.4.1.2 Analysis

The analysis will be conducted in the same way as the analysis in Section 7.3.1.5.

7.4.2 Response (no worsening and improvement) at Month 6 on BILAG-2004 disease activity index

7.4.2.1 Variables

The composite endpoint (response at Month 6 based on the BILAG-2004 disease activity index) is a binary endpoint based on two variables, as defined below.

BILAG-1

A responder (1) is defined as having no new BILAG A organ domain score and at most one new BILAG B organ domain score assessed for the nine body systems. A responder can only be assessed if the full information of all body systems is available.

Non-responders (0) are defined as having one or more new BILAG A organ domain scores or at least two or more BILAG B organ domain scores. In the event of incomplete data in at least one of the body systems, but sufficient information to fulfill the non-response criteria, the subject is considered to be a non-responder.

Subjects that fit none of the above criteria are assigned a missing value.

BILAG-2

A responder (1) is defined as having an improvement of at least one BILAG A organ domain score to either B, C or D or as having an improvement of at least one BILAG B organ domain score to C or D. A responder can only be assessed if the full information of all body systems is available.

A non-responder (0) is defined as having no improvement in any BILAG A or BILAG B organ domain scores. In the event of incomplete data in at least one of the body systems, but sufficient information to fulfill the non-response criteria, the subject is considered to be a non-responder.

Subjects without any BILAG A or BILAG B organ domain scores at baseline are defined as responders.

Composite endpoint

A responder (1) for the endpoint response at Month 6 based on the BILAG-2004 scale (alternative definition) is defined as a responder of both variables, as defined above. If at least one of the two variables equal a non-response, the subject is considered to be a non-responder (0). In the event of at least one of the two variables being missing, the subject is assigned a missing value, unless it is clear that the subject is a non-responder.

7.4.2.2 Analysis

The analysis will be conducted in the same way as the analysis in Section 7.3.1.5.

7.4.3 Response at Month 6 on SRI-5, -6, -7, -8

7.4.3.1 Variables

The binary response variables of these endpoints are derived as described in Section 7.3.1.2 with a reduction in mSLEDAI-2K of 5, 6, 7 or 8, instead of a reduction of 4.

For SRI-X (X = 5, 6, 7 or 8) subjects with a baseline value of less than X will be excluded from the analysis.

7.4.3.2 Analysis

The analysis will be conducted in the same way as the analysis in Section 7.3.1.5.

7.4.4 Occurrence of mild/moderate and severe flares from baseline up to Month 6

7.4.4.1 Variables

Derived data for this endpoint is provided by an external vendor. Data is categorized into mild/moderate or severe flares.

The definition of flares is provided in appendix 12 of the protocol [D-22.031].

7.4.4.2 Analysis

The number and percentage of subjects with no flare, mild/moderate flare and severe flare from baseline up to Month 6 overall as well as at every visit will be summarized by treatment group.

7.4.5 Time to first severe flare up to Month 6

7.4.5.1 Variables

The time to first severe flare during TP1, from baseline to Month 6 visit (in days) is defined as:

[Date of first severe flare – Date of treatment start date + 1] in days.

The start date of the first severe flare must be within TP1. Missing dates are imputed as follows:

- Day missing: Impute first day of the month or if earlier than first study drug intake, impute day of first study drug intake.
- Day and month missing: If the year is in the interval of (First study drug intake; Month 6) impute the first study drug intake date, otherwise keep as missing.
- If the date is completely missing, then include severe flare in the analysis and set the date to the first study drug intake date.

For subjects without any severe flares, the time to the first severe flare is censored at the Month 6 visit date or at the time of last available observation without any severe flares in TP1 if the subject discontinues study prior to Month 6.

Subjects with a severe flare during TP1 are considered as having an event ('1'), censored subjects as having no event ('0').

7.4.5.2 Analysis

The number of subjects with events and subjects with censored observations will be presented by treatment group.

A Kaplan-Meier plot will be produced showing all five treatment arms and p-values.

The treatment effect will be estimated using a stratified Cox proportional hazard model (displaying hazard ratios and 95% CI), stratified by OCS and mSLEDAI-2K (from IXRS). Hazard ratios and 95% CI will also be displayed in the Kaplan-Meier plot.

```
* KM;
proc lifetest;
 strata treatment;
 id subjid;
 time time*censor(1);
 ods select productlimitestimates quartiles;
run;

* cox proportional hazard model;
proc phreg;
 class treatment (ref="placebo");
 model time*censor(1) = treatment / ties=exact rl;
 strata ocs sledai_sc;
 ods select ParameterEstimates;
run;
```

The analysis will be conducted for data collected during TP1 up to both Month 6 and EOT.

7.4.6 Time to first flare up to Month 6

7.4.6.1 Variables

Variables for the endpoint 'time to first flare from baseline to Month 6' are derived exactly in the same way as in the previous section, with the only difference that all flares instead of only severe flares are included. Variables are derived up to EOT (during TP1) and up to Month 6.

7.4.6.2 Analysis

The Cox proportional hazards model will be repeated as described in Section 7.4.5.2 for data collected during TP1 up to both Month 6 and EOT.

7.4.7 Change from baseline to Month 6 in PGA score

7.4.7.1 Variables

The absolute change from baseline to Month 6 in PGA score is derived as:

Change in PGA = PGA score at Month 6 – PGA score at baseline.

In the event of missing values at one of the assessments, the variable is set to missing.

7.4.7.2 Analysis

An MMRM model will be used to analyze this endpoint including all monthly visits (similar to primary efficacy analysis in Section 7.2.5).

The following fixed effects will be included in the model: PGA baseline value, the two stratification factors (OCS and mSLEDAI-2K from IXRS), treatment group, month, treatment group by month interaction and PGA baseline value by month interaction.

7.5 Exploratory endpoints

All exploratory endpoints will be summarized descriptively and listed using the FAS or FAS-TP2 unless otherwise stated.

Additional analyses for the exploratory endpoints are described in the sections below.

Exploratory endpoints will be analyzed from baseline up to a maximum of 12 months on all available assessments according to 2 Groups:

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

A time window approach will be applied to the endpoints where data will be analyzed at protocol-mandated visits [as defined in Section 5.4.4].

The display of treatment groups in the summary tables is as defined in Section 5.4.3. Group 1 will be analyzed based on 5 treatment groups (Placebo, 0.5, 1, 2, 4 mg), whereas Group 2 will be analyzed based on 6 treatment groups (Placebo, 0.5, 1, 2, 4 mg / 2 mg and 4 mg / placebo).

7.5.1 Sustained mSLEDAI-2K response defined as a reduction of at least [redacted]

7.5.1.1 Variables

A binary response variable is derived for this endpoint. The following criteria apply for a responder (1):

- Subject must have at least [redacted] mSLEDAI-2K assessments [redacted]
- Subject must have a reduction of the mSLEDAI-2K of at least [redacted]
- Subject must have a reduction of the mSLEDAI-2K of at least [redacted]

[redacted]

7.5.1.2 Analysis

This endpoint will only be analyzed for Group 1 using the FAS with a logistic regression model.

The logistic regression model will include the treatment group [as defined in Section 5.4.3.1] and will be stratified by the OCS and mSLEDAI-2K stratification variables (from IXRS).

The estimates of the ORs between each cenerimod dose group and placebo will be reported with their 95% CIs. In addition, the proportion of responders will be reported by treatment group.

7.5.2 Change from baseline to each post-baseline assessment up to Month 12 in mSLEDAI-2K score

7.5.2.1 Variables

Group 1

The variable is derived as defined in the primary endpoint Section 7.2.1, for each visit up to Month 12.

Group 2

The variable is derived as defined in the primary endpoint Section 7.2.1 for each visit from Month 6 up to Month 12 based on the TP2 baseline value for all subjects in FAS-TP2.

7.5.2.2 Analysis

Group 1

An MMRM analysis will be performed as described in Section 7.2.5, including visits up to Month 12 using 5 treatment groups as defined in Section 5.4.3.3.

Group 2

An MMRM analysis will be performed similar to the one described in Section 7.2.5, but only including data from Month 7 up to Month 12 and from treatment groups *Cenerimod 2 mg / Ex-4 mg* and *Placebo / Ex-4 mg*. The model will include treatment group, month, TP2 baseline mSLEDAI-2K score, treatment group by month interaction and TP2 baseline mSLEDAI-2K score by month interaction as fixed effects.

All other aspects of the model are as described in Section 7.2.5.

7.5.3 Response at each post-baseline assessment on the mSLEDAI-2K

7.5.3.1 Variables

Group 1

The variable is derived as in Section 7.4.1.1 for each visit up to Month 12.

Group 2

The variable is derived as in Section 7.4.1.1 for each visit from Month 6 up to Month 12 based on the TP2 baseline value for all subjects in FAS-TP2.

7.5.3.2 Analysis

Group 1

A repeated measurements GLMM model for binary response variables will be performed as described in Section 7.3.1.5 based on 5 treatment groups as described in Section 5.4.3.3.

Group 2

A repeated measurements GLMM model for binary response variables will be performed as described in Section 7.3.1.5. The model will be fitted including data from Month 7 up

to Month 12 and from treatment groups *Cenerimod 2 mg / Ex-4 mg* and *Placebo / Ex-4 mg*. The model will include treatment group, month, TP2 baseline mSLEDAI-2K score, treatment group by month interaction and TP2 baseline mSLEDAI-2K score by month interaction as fixed effects.

All other aspects of the model are as described in Section 7.3.1.5.

7.5.4 Response (no worsening and improvement) at each post-baseline assessment on BILAG-2004 disease activity index

7.5.4.1 Variables

Group 1

The variable is derived as defined in Section 7.4.2 for each visit up to Month 12.

Group 2

The variable is derived as defined in Section 7.4.2 for each visit from Month 6 up to Month 12 based on the TP2 baseline value for all subjects in FAS-TP2.

7.5.4.2 Analysis

Group 1

A repeated measurements GLMM model for binary response variables will be performed as described in Section 7.3.1.5 based on 5 treatment groups as described in Section 5.4.3.3.

Group 2

A repeated measurements GLMM model for binary response variables will be performed, as described in Section 7.3.1.5. The model will be fitted including data from Month 7 up to Month 12 and from treatment groups *Cenerimod 2 mg / Ex-4 mg* and *Placebo / Ex-4 mg*. The model will include treatment group, month and treatment group by month interaction as fixed effects.

All other aspects of the model are as described in Section 7.3.1.5.

7.5.5 Response at each post-baseline assessment on SRI-4, -5, -6, -7, -8

7.5.5.1 Variables

Group 1

The variables are derived as defined in Sections 7.3.1.2 and 7.4.3.1 for each visit from Month 1 up to Month 12.

Group 2

The variables are derived as defined in Sections 7.3.1.2 and 7.4.3.1 for each visit from Month 6 up to Month 12 based on the TP2 baseline value for all subjects in FAS-TP2.

7.5.5.2 Analysis

Group 1

A repeated measurements GLMM model for binary response variables will be performed as described in Section 7.3.1.5 based on 5 treatment groups as described in Section 5.4.3.3.

Group 2

A repeated measurements GLMM model for binary response variables will be performed, as described in Section 7.3.1.5. The model will be fitted including data from Month 7 up to Month 12 and from treatment groups *Cenerimod 2 mg / Ex-4 mg* and *Placebo / Ex-4 mg*. The model will include treatment group, month and treatment group by month interaction as fixed effects.

All other aspects of the model are as described in Section 7.3.1.5.

7.5.6 Change from baseline to each post-baseline assessment in PGA score

7.5.6.1 Variables

Group 1

The variable is derived as defined in Section 7.4.7.1 for each visit from Month 1 up to Month 12.

Group 2

The variable is derived as defined in Section 7.4.7.1 for each visit from Month 6 up to Month 12 based on the TP2 baseline value for all subjects in FAS-TP2.

7.5.6.2 Analysis

Group 1

The analysis will be based on an MMRM model, similar to the one used for the primary analysis [Section 7.2.5] based on 5 treatment groups as described in Section 5.4.3.3.

Group 2

The analysis will be based on an MMRM model, similar to the one used for the primary analysis [Section 7.2.5]. The model will be fitted including data from Month 7 up to Month 12 and from treatment groups *Cenerimod 2 mg / Ex-4 mg* and *Placebo / Ex-4 mg*. The model will include treatment group, month, TP2 baseline PGA score, treatment group by month interaction and TP2 baseline PGA score by month interaction as fixed effects.

All other aspects of the model are as described in Section 7.2.5.

7.5.7 Occurrence of flares and severe flares at each post-baseline assessment

7.5.7.1 Variables

Derived data for this endpoint is provided by an external vendor. Data will be categorized into mild/moderate or severe flares.

The definition of flares is provided in appendix 12 of the protocol [D-22.031].

7.5.7.2 Analysis

Group 1

Data will be analyzed descriptively as described in Section 7.4.4.2 for data up to Month 12 using treatment groups as described in Section 5.4.3.3.

Group 2

Data will be analyzed descriptively for all subjects in FAS-TP2 as described in Section 7.4.4.2 using treatment groups as defined in Section 5.4.3.2 for data from baseline TP2 up to Month 12.

7.5.8 Time to first severe flare from baseline to Month 12

7.5.8.1 Variables

Group 1

The variable is derived as defined in Section 7.4.5.1, for visits up to EOT (including TP2) and up to Month 12.

Group 2

The variable is derived as defined in Section 7.4.5.1, from the Month 6 visit up to EOT and up to Month 12 for all subjects in FAS-TP2. The censoring is derived from start of TP2, instead of start of TP1.

7.5.8.2 Analysis

Group 1

A Cox proportional hazards model will be performed as described in Section 7.4.5.2 based on 5 treatment groups as described in Section 5.4.3.3 for data up to EOT and up to Month 12.

Group 2

A Cox proportional hazards model will be performed with treatment as a factor, only including treatment groups *Cenerimod 2 mg / Ex-4 mg* and *Placebo / Ex-4 mg*.

7.5.9 Time to first flare from baseline to Month 12

7.5.9.1 Variables

Group 1

The variable is derived as defined in Section 7.4.6.1, for visits up to EOT + 180 days (including TP2) and up to Month 12.

Group 2

The variable is derived as defined in Section 7.4.6.1, from the Month 6 visit up to EOT + 180 days and up to Month 12 for all subjects in FAS-TP2. The censoring is derived from start of TP2, instead of start of TP1.

7.5.9.2 Analysis

Group 1

A Cox proportional hazards model will be performed as described in Section 7.4.6.2 based on 5 treatment groups as described in Section 5.4.3.3 for data up to EOT and up to Month 12.

Group 2

A Cox proportional hazards model will be performed with treatment as a factor, only including treatment groups *Cenerimod 2 mg / Ex-4 mg* and *Placebo / Ex-4 mg*.

7.5.10 Change from baseline to each post-baseline assessment up to Month 12 in prednisone or equivalent dose

7.5.10.1 Variables

Group 1

Steroids are collected on the Previous/Concomitant Medications eCRF page. OCS will be identified using the WHODrug Global B3/C3-format Standardized Drug Grouping named "Corticosteroids" and with CM.CMROUTE equal "ORAL". Doses that are not taken daily will be transformed according to CM.CMDOSFRQ. OCS are converted to prednisone equivalent doses using the table in the protocol, appendix 1 [D-22.031]. If subjects are taking OCS during the study that are not covered in the table in the protocol, conversion factors are retrieved from the literature.

The prednisone or equivalent dose at each visit from baseline up to Month 12 will be derived as the monthly average of the daily prednisone or equivalent dose as shown in Table 9.

Table 9 Daily prednisone or equivalent doses used for derivation of monthly scores

Monthly score	First treatment day	Last treatment day
Baseline	–30	–1
Month 1	1	30
Month 2	31	60
Month 3	61	90
Month 4	91	120
Month 5	121	150
Month 6	Month 6 visit* – 29 days	Month 6 visit
Month 7	Month 6 visit + 1 day	Month 6 visit + 30 days
Month 8	Month 6 visit + 31 day	Month 6 visit + 60 days
Month 9	Month 6 visit + 61 day	Month 6 visit + 90 days
Month 10	Month 6 visit + 91 day	Month 6 visit + 120 days
Month 11	Month 6 visit + 121 day	Month 6 visit + 150 days
Month 12	Month 6 visit + 151 day	Month 6 visit + 180 days

* If a subject has a visit recorded after Month 6 but the Month 6 visit was not done, Month 6 visit will be replaced by Day 180.

It may be noted that for subjects with a Month 6 visit performed earlier than Day 180, there will be an overlap between the 29 days used to derive the Month 5 monthly score and the 29 days used to derive the Month 6 monthly score.

The absolute change in prednisone or equivalent dose from baseline (in TP1) is computed as follows:

Change in prednisone or equivalent dose = Prednisone or equivalent dose at Visit X – prednisone or equivalent dose at baseline (in TP1).

7.5.10.2 Analysis

Group 1

The change in prednisone or equivalent dose during TP1 will be analyzed descriptively, by visit and treatment groups as defined in Section 5.4.3.1. In addition, a figure by visit and treatment group will be produced, containing the change in prednisone or equivalent dose.

The change in prednisone or equivalent dose during TP1 and TP2 will be analyzed descriptively, by visit and treatment groups as defined in Section 5.4.3.3.

7.6 Analysis of PRO/QoL variables

A time window approach will be applied to the PRO endpoints [as defined in Section 5.4.4]. Data will be listed using the FAS.

All PRO endpoints will be analyzed during TP1 by treatment groups as defined in Section 5.4.3.1 and during TP1 and TP2 by treatment groups as defined in Section 5.4.3.3.

7.6.1 Change from baseline to each post-baseline assessment in FACIT-Fatigue Scale score

The FACIT-Fatigue Scale is collected at Randomization, Month 3, Month 6, Month 9 and Month 12/premature EOT. The FACIT-Fatigue Scale score is based on a questionnaire with 13 questions.

7.6.1.1 Variables

Calculation of FACIT-Fatigue Scale score

The FACIT-Fatigue Scale score will be derived as described in Appendix 12.4.

The absolute change in FACIT-Fatigue Scale score is computed as follows:

Change in FACIT-Fatigue Scale score = FACIT-Fatigue Scale score at Visit X – FACIT-Fatigue Scale score at baseline (in TP1)

7.6.1.2 Analysis

The change in FACIT-Fatigue Scale score will be analyzed descriptively, by visit and treatment group using the FAS.

A figure of the change in FACIT-Fatigue Scale score over time will be produced using the FAS, by visit and treatment group.

7.6.2 Change from baseline to each post-baseline assessment in PGIS-F

7.6.2.1 Variables

[redacted]. The PGIS-F is collected as defined in the visit and assessment schedule [see Appendix 12.1].

7.6.2.2 Analysis

The change from baseline to each post-baseline assessment in the PGIS-F will be analyzed descriptively by visit and treatment group using the FAS with a shift table.

7.6.3 PGIC-F score at each post-baseline assessment

7.6.3.1 Variables

[redacted]

The PGIC-F is collected as defined in the visit and assessment schedule [see Appendix 12.1].

7.6.3.2 Analysis

The PGIC-F will be analyzed descriptively by visit and treatment group using the FAS with summary statistics as defined in Section 9.1 for categorical variables.

7.6.4 Change from baseline to each post-baseline assessment in SF-36v2™

SF-36v2™ data is collected using a paper CRF. Data is collected at Randomization, Month 6, Month 9 and Month 12 / premature EOT.

According to the questionnaire manual [Ware 2000], the following scores are considered:

- SF-36v2™ domain scores (0–100 scale): physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health.
- SF-36v2™ domain scores norm-based: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health.
- SF-36v2™ PCS and MCS measures norm-based.
- SF-36v2™ reported health transition score.

7.6.4.1 Variables

The SF-36v2™ is a multi-purpose, short-form health survey with 36 questions. It yields an 8-scale profile of the functional health and well-being scores (i.e., physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health) as well as psychometrically based physical and mental health summary measures and a preference-based health utility (health rated as ‘much better now than one year ago’, ‘somewhat better now than one year ago’, ‘about the same as one year ago’, ‘somewhat worse now than one year ago’, and ‘much worse now than one year ago’).

The following scores/measures are derived inhouse as described in the SF-36v2™ scoring manual using 1998 US population norms [Ware 2000] and detailed in Appendix 12.3 for the analysis:

- SF-36v2™ domain scores transformed to a 0–100 scale.
- SF-36v2™ domain scores norm-based (also known as T-scores).
- SF-36v2™ PCS and MCS measures norm-based (also known as T-scores).
- SF-36v2™ reported health transition score.

Missing items of incomplete questionnaires are imputed as described in Appendix 12.3. If, after applying imputation rules, the value at a given time point is missing (domain scores or component summary measures) then the value is considered missing.

Except for the reported health transition score (which is expressed as a subjective change in the question), the absolute change from baseline is defined as:

Change of SF-36v2™ score = SF-36v2™ individual score at visit – SF-36v2™ individual score at baseline

Baseline is defined as the last valid assessment prior to first study drug intake (by time and date).

7.6.4.2 Analysis

SF-36v2™ data will be analyzed using the FAS by visit and treatment group.

Summary statistics, by visit and treatment group, will be produced for all sub-scores and normalized sub-scores (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health, PCS and MCS). The health transition score will only be described at Month 12, and will be listed for all visits. Changes from baseline will be summarized for sub-scores and normalized sub-scores.

7.6.5 Change from baseline to each post-baseline assessment in the Lupus QoL questionnaire

The Lupus QoL questionnaire will be collected at Randomization, Month 6, Month 9 and Month 12/premature EOT. The Lupus QoL score is based on a questionnaire with 34 questions.

7.6.5.1 Variables

Calculation of Lupus QoL score

[redacted]1.

The Lupus QoL consists of 34 items in eight domains. The number of items in each domain and the item numbers that refer to each domain are shown in Table 10.

Table 10 Lupus QoL domains

7.6.5.2 Analysis

The change in Lupus QoL score will be analyzed descriptively, by visit and treatment group, using the FAS. A figure of the change in Lupus QoL score over time will be produced using the FAS, by visit and treatment group.

7.6.6 Change of mucocutaneous and musculoskeletal score from baseline (TP1) up to Month 12

7.6.6.1 Variables

The mucocutaneous score is defined as the weighted sum of each of the individual descriptors for the applicable organ class, i.e., mucosal ulcers, rash, and alopecia. The score is computed by summing up the standardized results for each descriptor.

The musculoskeletal score is defined as the weighted sum of each of the individual descriptors for the applicable organ class, i.e., arthritis and myositis. The score is computed by summing up the standardized result for each descriptor.

The mucocutaneous and musculoskeletal score is defined as the sum of the mucocutaneous and the musculoskeletal scores (computed above).

The absolute change from baseline (TP1) is computed as:

Change in mSLEDAI-2K sub-score = mSLEDAI-2K sub-score at Visit X – mSLEDAI-2K sub-score at baseline (in TP1).

7.6.6.2 Analysis

The change in mucocutaneous and musculoskeletal score will be analyzed descriptively, by visit and treatment group, using the FAS.

7.7 Analysis of pharmacokinetic variables

See Section 6.10.

8 SAFETY VARIABLES AND ANALYSES

8.1 Overview of safety analyses including subgroup analyses

8.1.1 Safety endpoints

The following endpoints are defined according to protocol:

- Occurrence of TEAEs/SAEs, and AESIs [see protocol appendix 5, D-22.031].
- Occurrence of AEs leading to premature discontinuation of study treatment.
- Changes in 12-lead ECG variables (HR, PR, QRS, QT, QT corrected for HR on the basis of QTcB and QTcF), from baseline to each post-baseline assessment up to EOS (i.e., each post-dose time point on Day 1 / re-initiation and each post-dose analysis visit up to EOS) for each parameter.
- Occurrence of treatment-emergent 12-lead ECG notable abnormalities (e.g., HR, PR, QTc) [see protocol appendix 7, D-22.031].
- Occurrence of treatment-emergent 12-lead ECG abnormal findings.
- Change in supine SBP/DBP from baseline to each post-baseline assessment up to EOS (i.e., each post-dose time point on Day 1 / re-initiation and each post-dose analysis visit up to EOS).
- Change in FEV_1 and FVC from baseline to each post-baseline assessment up to EOS.
- Occurrence of treatment-emergent decrease of FEV_1 or FVC > 15% from baseline values at any post-baseline assessment.
- Change in laboratory parameters (hematology, blood chemistry, and urinalysis) from baseline to each post-baseline assessment up to EOS.

- Occurrence of treatment-emergent laboratory notable abnormalities [see protocol appendix 7, D-22.031].
- Change in body weight from baseline up to EOS.
- Change in left ventricular ejection fraction as assessed by Standard 2D/Doppler echocardiography from Screening to Month 6 in subjects randomized to ancillary echocardiography study.
- Occurrence of abnormalities as assessed by Standard 2D/Doppler echocardiography from Screening to Month 6 in subjects randomized to ancillary echocardiography study.

8.2 Adverse events

An AE is any event reported by the investigator on the Adverse Event eCRF page.

All AEs will be coded using MedDRA (most current version at time of database closure/snapshot).

AEs are classified according to the period of occurrence of the event. Periods are defined as:

- TEAEs
- AEs with onset during TP1
- AEs with onset during TP2

A more detailed description of rules for assigning AEs to the different periods is described below.

All AE tables will be summarized using the SAF. AE listings (all AEs, AEs leading to premature discontinuation of study treatment, SAEs, AESIs) will be produced using the SAF. A separate listing will be produced using the SCR to present AEs for non-treated subjects.

8.2.1 Variables

AEs are classified as 'Treatment-emergent AEs' if the start date of the AE is on or after the date of first study drug intake (by time and date) up to EOT + 180 days (inclusive).

AEs with onset during TP1 are defined in the interval:

[First study drug intake (by time and date); Month 6 visit or EOT
(if EOT date is on or before Month 6 visit date)]

AEs with onset during TP2 are defined in the interval:

[Month 6 visit + 1 day; EOT].

Any AE prior to start of treatment (by time and date) in TP1 and AEs 121 days or more after EOT are considered non-treatment-emergent AEs.

TEAEs on Day 1 are reported up to 24 hours after first study drug intake in TP1 and on or after the time of first study drug intake.

TEAEs on the day of re-initiation are defined in the same way, but for the day of the re-initiation.

8.2.1.1 Missing values

Missing or partial dates for TEAEs are imputed as follows for the purpose of the treatment-emergent definition:

- AE start day missing: If the month and year is on or after the time and date of the first study drug intake month and year, and before or during the month and year of EOT + 180 days, consider the AE as treatment-emergent and impute the first day of the month, and if it is earlier than the first study drug intake, impute the first study drug intake date.
- AE start day and month missing: If the year is the same year as the year of first study drug intake or later, and if the year is prior to or in the same year as the year of EOT + 180 days, consider the AE as treatment-emergent and impute the date of first study drug intake.
- If the AE start date is completely missing then the AE is considered to be treatment-emergent (for TP1, but not for TP2).

If the time of an AE occurring on the day of first study drug intake is not recorded, the AE is considered to be treatment-emergent.

The same rule applies for AEs on the day of re-initiation.

8.2.2 Analysis

An overview of AEs with onset during TP1 will be provided, showing number and percentage of subjects with at least one:

- AE with onset during TP1
- Treatment-emergent AE on day of first study drug intake
- Treatment-emergent AE on day of re-initiation
- AE with onset during TP1 related to study treatment
- Severe AE with onset during TP1
- AE of special interest with onset during TP1
- SAE with onset during TP1
- SAE related to study treatment with onset during TP1

- Fatal AE with onset during TP1
- AE leading to study drug discontinuation with onset during TP1
- AE leading to study drug interruption with onset during TP1

An overview of AEs with onset during TP2 will be provided, showing number and percentage of subjects with at least one:

- AE with onset during TP2
- AE with onset during TP2 related to study treatment
- Severe AE with onset during TP2
- AE of special interest with onset during TP2
- SAE with onset during TP2
- SAE related to study treatment with onset during TP2
- Fatal AE with onset during TP2
- AE leading to study drug discontinuation with onset during TP2
- AE leading to study drug interruption with onset during TP2

An overview of TEAEs will be provided, showing number and percentage of subjects with at least one:

- Treatment-emergent AE
- Treatment-emergent AE related to study treatment
- Treatment-emergent severe AE
- Treatment-emergent AE of special interest
- Treatment-emergent SAE
- Treatment-emergent SAE related to study treatment
- Treatment-emergent fatal AEs
- AE leading to study drug discontinuation
- AE leading to study drug interruption

AEs will be summarized by presenting the number and percentage of subjects with at least one event, having an AE in each primary SOC, and having each individual AE (PT), for each treatment group.

AEs will be sorted by descending frequency in the highest dose group, then second highest dose group, and so on until the placebo group, and then alphabetically.

Summary tables will be provided for the following:

- AEs with onset during TP1 (by SOC and PT)
- AEs with onset during TP2 (by SOC and PT)
- TEAEs (by SOC and PT)
- TEAEs (by PT)
- TEAEs on day of first study drug intake (by SOC and PT)
- TEAEs on day of re-initiation (by SOC and PT)
- AEs related to study treatment with onset during TP1 (by SOC and PT)
- AEs related to study treatment with onset during TP2 (by SOC and PT)
- TEAEs related to study treatment (by SOC and PT)
- AEs with onset during TP1 (by SOC, PT and intensity)
- AEs with onset during TP2 (by SOC, PT and intensity)
- TEAEs (by SOC, PT and intensity)
- AEs of special interest with onset during TP1 (by SOC and PT)
- AEs of special interest with onset during TP2 (by SOC and PT)
- TEAEs of special interest (by SOC and PT)
- AEs of special interest with onset during TP1 (by category and PT)
- AEs of special interest with onset during TP2 (by category and PT)
- TEAEs of special interest (by category and PT)
- SAEs with onset during TP1 (by SOC and PT)
- SAEs with onset during TP2 (by SOC and PT)
- TESAEs (by SOC and PT)
- Treatment-emergent deaths and SAEs (by SOC and PT)
- Non-serious TEAEs (frequency threshold ≥ 5%; by SOC and PT)
- TESAEs (by PT)
- SAEs related to study treatment with onset during TP1 (by SOC and PT)
- SAEs related to study treatment with onset during TP2 (by SOC and PT)
- TESAEs related to study treatment (by SOC and PT)
- Fatal AEs with onset during TP1 (by SOC and PT)
- Fatal AEs with onset during TP2 (by SOC and PT)
- Fatal TEAEs (by SOC and PT)
- AEs leading to temporary interruption of study treatment with onset during TP1 (by SOC and PT)

- AEs leading to temporary interruption of study treatment with onset during TP2 (by SOC and PT)
- AEs leading to temporary interruption of study treatment (by SOC and PT)
- AEs leading to premature discontinuation of study treatment with onset during TP1 (by SOC and PT)
- AEs leading to premature discontinuation of study treatment with onset during TP1 (by PT)
- AEs leading to premature discontinuation of study treatment with onset during TP2 (by SOC and PT)
- AEs leading to premature discontinuation of study treatment with onset during TP2 (by PT)
- AEs leading to premature discontinuation of study treatment (by SOC and PT)

8.2.2.1 AESIs

AESIs include important identified or potential risks of the treatment with cenerimod, the known class effects or events that may be related to SLE comorbidities (e.g., cardiovascular AEs).

AESIs include the following safety categories:

- Effect on HR- and rhythm-related AEs
- Hypotension-related AEs
- Hypertension-related AEs
- Hepatobiliary disorder- / liver enzyme abnormality-related AEs
- Pulmonary-related AEs
- Macular edema- / Eye disorder-related AEs
- Infection-related AEs
- Malignancy (skin)-related AEs
- Malignancy (non-skin)-related AEs
- Cardiovascular-related AEs

AESIs are identified via PTs provided by the Idorsia Drug Safety department [see Appendix 12.2].

8.3 Death

8.3.1 Variables

Data are taken from the Death eCRF page.

8.3.2 Analysis

Deaths will be summarized using the SAF and listed using the SCR Actual treatment group will be displayed in the listing. Deaths will be summarized by treatment group, SOC and PT.

8.4 Laboratory tests

Laboratory test results are transferred from the central laboratory or, if assayed locally, entered in local laboratory eCRF (in exceptional cases). Local laboratory data will only be listed (as local laboratory data is only requested in specific rare circumstances for medical evaluation of an individual subject).

Laboratory assessments are performed at each scheduled visit from Screening up to the EOS visit (except FU2, FU3, FU3a, and FU3b), and at unscheduled visits if required.

A time window approach will be applied to the laboratory data [as defined in Section 5.4.4].

8.4.1 Measurements

The following parameters are assayed at any scheduled visit according to the protocol:

Hematology:

- Hemoglobin
- Hematocrit, mean corpuscular hemoglobin, mean corpuscular volume, and mean corpuscular hemoglobin concentration
- Erythrocyte count (reticulocyte count)
- Leukocyte count with differential counts (only available after database lock)
- Platelet count

Blood chemistry:

- Aspartate aminotransferase and alanine aminotransferase, alkaline phosphatase, total and direct bilirubin, lactate dehydrogenase
- Creatinine
- Blood urea nitrogen
- Uric acid
- Glucose
- Cholesterol, triglycerides
- Sodium, potassium, chloride, calcium
- Protein, albumin

Urinalysis (including but not limited to):

- pH

- Glucose
- Proteins
- Blood
- Leukocytes

Tests for tuberculosis, viral serology tests (Hepatitis B surface antigen, Hepatitis C antibodies, HIV1 and HIV2 antibodies, varicella-zoster virus IgG antibodies), coagulation tests (prothrombin time, international normalized ratio, activated partial thromboplastin time, urine-protein-to-creatinine ratio), other laboratory tests in the event of infection and pregnancy tests are also carried out during the study.

8.4.2 Variables

The absolute change and percent change from baseline in laboratory parameters (hematology, blood chemistry, and urinalysis) at each post-baseline analysis visit up to EOS is calculated as follows:

- Absolute change in laboratory parameters = Laboratory value at Visit X – Laboratory value at baseline (TP1)
- Percent change in laboratory parameters = (Laboratory value at Visit X – Laboratory value at baseline [TP1]) / Laboratory value at baseline (TP1) × 100

Absolute and percent changes are also derived based on the TP2 baseline.

Laboratory test abnormalities are defined as summarized in protocol appendix 7, for the following periods:

- During TP1: up to Month 6 for subjects who complete TP1 on treatment and up to EOT for subjects who discontinue study treatment during TP1.
- During TP2: up to EOT.
- Treatment-emergent (combining TP1 and TP2 data): up to EOT + 180 days.

8.4.3 Analysis

Laboratory parameters will be summarized using the SAF (for TP1 and for TP1+TP2 combined) and using the SAF-TP2 (for TP2) by visit and treatment group [as defined in Section 5.4.3]. Data will be displayed in SI units as provided by the central laboratory.

Treatment-emergent marked laboratory abnormalities (up to EOT + 180 days) as well as marked laboratory abnormalities during TP1 and during TP2 will be summarized by treatment group.

A subject will be counted only once in the most severe category of a given parameter. However, it is possible that, for a given parameter, the same subject is counted as a high marked abnormality for an observed value and as a low marked abnormality for a different

observed value. An abnormality is only counted as treatment-emergent if the criterion itself and all more severe criterion for the same parameter were not already present at baseline.

Percentages will be based on the number of subjects at risk, i.e., those not meeting the criterion or a more severe criterion for the same parameter at baseline (or having a missing baseline value) and having at least one post-baseline value for a given parameter. For criteria that are not only based on absolute values but also on changes from baseline, subjects with a missing baseline value are not included in the number of subjects at risk.

A standard laboratory listing will be produced using the SAF containing all central and local laboratory data collected in the database. Local laboratory data will only be listed.

8.5 Spirometry

Spirometry measurements are performed every three months during the double-blind study treatment period and at the EOS visit.

Spirometry test results will be transferred from a vendor including information on the quality of the measurements.

A time window approach will be applied to the spirometry data [as defined in Section 5.4.4].

8.5.1 Measurements

FEV_1 (in L) and FVC (in L) are assessed in this study.

The percent predicted FEV_1 and FVC is computed based on the formula defined by Quanjer [Quanjer 1993].

8.5.2 Variables

8.5.2.1 Definition absolute change and percent change from baseline (TP1)

The absolute change from baseline for FEV_1, FVC, percent predicted FEV_1 and percent predicted FVC is calculated as follows:

- Change from baseline = FEV_1 at post-baseline visit – FEV_1 at baseline
- Change from baseline = FVC at post-baseline visit – FVC at baseline

Percent change from baseline for FEV_1, FVC, percent predicted FEV_1 and percent predicted FVC is calculated as follows:

- Percent change from baseline = (FEV_1 at post-baseline visit – FEV_1 at baseline) / FEV_1 at baseline × 100
- Percent change from baseline = (FVC at post-baseline visit – FVC at baseline) / FVC at baseline × 100

Percent change from baseline expressed as percent of predicted baseline for FEV_1 and FVC is calculated as follows:

- Percent change from baseline = (FEV_1 at post-baseline visit – FEV_1 at baseline) / predicted FEV_1 at baseline × 100
- Percent change from baseline = (FVC at post-baseline visit – FVC at baseline) / predicted FVC at baseline × 100

8.5.2.2 Definition absolute change and percent change from baseline (TP2)

The absolute change and percent change from baseline (TP2) is calculated in the same way as described above.

8.5.2.3 Decrease of (percent predicted) FEV_1 or FVC > 15% from baseline

A percent change decrease > 15% is defined for the following periods:

- During TP1: up to Month 6 for subjects who complete TP1 on treatment and up to EOT for subjects who discontinue study treatment during TP1.
- During TP2: up to EOT.
- Treatment-emergent (combining TP1 and TP2 data): up to EOT + 180 days.

8.5.3 Analysis

Spirometry outputs will be produced using the SAF (for TP1 and for TP1+TP2) and SAF-TP2 (for TP2).

Observed values, changes from baseline and percent changes from baseline of FEV_1 and FVC will be summarized by visit and treatment group, during TP1 using the FAS, during TP2 using the FAS-TP2, and combining TP1 and TP2 for each post-baseline assessment up to EOS using the FAS.

For percentage changes from baseline, summary statistics will be derived from the geometric mean of the ratio to baseline, and from the geometric mean of the ratio to predicted value at baseline for the percentage change expressed as percent of predicted baseline. Geometric mean will be computed and transformed into a percentage change by using the transformation x – > ((x-1) × 100) as described in Section 8.9.2.

The CV of the geometric mean will also be presented [see Section 8.9.2 for calculation].

All outputs defined above will be repeated for percent predicted FEV_1 and FVC.

Summary statistics will be produced showing the number of subjects with a treatment-emergent decrease of at least 15% from baseline for FEV_1 and FVC and percent predicted FEV_1 and FVC. Decreases during TP1 and during TP2 will be summarized as well.

Spirometry data will be listed using the SAF.

8.6 Electrocardiography

The 12-lead ECG measurements and qualitative ECG findings (e.g., rhythm, ectopy, conduction and morphology) are provided by the ECG central reader, along with the overall interpretation of the ECG (Normal/Abnormal).

ECG Holter monitoring data and findings are also provided by a central reader.

8.6.1 Measurements

12-lead ECG is measured at visits defined in the visit and assessment schedule [see Appendix 12.1].

The following parameters will be evaluated: HR (bpm), PR (ms), QRS (ms), QT (ms), QTc (ms), and any ECG findings. QTc (ms) is calculated according to Bazett's and Fridericia's formula. Data is received in derived form by the vendor.

A time window approach will be applied to the ECG data [as defined in Section 5.4.4].

ECG Holter monitoring is performed for 24 hours at Visit 2 (Randomization).

8.6.2 Variables

8.6.2.1 Change from baseline in 12-lead ECG

Change of ECG measurements is derived on the day of first study drug intake, on the day of re-initiation and generally from the baseline (in TP1) to each pre-dose assessment at any visit during the conduct of the study. Changes are derived for any ECG parameter provided by the vendor (mean HR, PR interval, QRS duration, QT interval, QTcB and QTcF interval).

The intra-day change is defined for the day of first study drug intake and the day of re-initiation, by hour:

Hourly intra-day change = Value at hourly post-dose assessment – value at pre-dose assessment.

ECG values at the pre-dose assessment must have been assessed on the day of first study drug intake / day of re-initiation, otherwise they are considered to be missing. Some subjects might stay longer in hospital than the expected 6 hours. Intra-day changes are also calculated for assessments performed later than 6 hours after first study drug intake.

Changes compared to a derived baseline value are defined as:

Change = Value at post-baseline visit (pre-dose) – derived baseline value.

The derived baseline value is defined as the last valid value measured prior to first study drug intake in TP1 (by date and time). For HR, the mean ECG HR is used to derive the baseline value. For the remaining ECG parameters (PR interval, QRS duration, QT

interval, QTcB and QTcF interval) aggregate values are provided by the ECG central reader that are used to derive the baseline value.

Changes from baseline are also derived based on the TP2 baseline.

8.6.2.2 Notable abnormalities (12-lead ECG)

Table 11 Notable abnormalities in ECG parameters

Analysis parameter	Analysis variable(s)	Analysis criterion
QTcB (ms) and QTcF (ms)	Analysis value	- Value > 450 and ≤ 480 (male), > 470 and ≤ 480 (female) - Value > 480 and ≤ 500 - Value > 500 and ≤ 520 (female) - Value > 500 (male), > 520 (female)
	Change from baseline	- Increase from baseline > 30 and ≤ 60 - Increase from baseline > 60
	Analysis value and change from baseline	- Value > 450 and increase from baseline > 30 and ≤ 60 - Value > 450 and increase from baseline > 60
Heart rate (bpm)	Analysis value	- Value < 40
PR duration (ms)	Analysis value	- Value > 200
	Change from baseline	- Increase from baseline > 20
	Analysis value and change from baseline	- Value > 200 and increase from baseline > 20

bpm = beats per minute; ECG = electrocardiogram; QTcB = QT interval corrected for heart rate using Bazett's formula; QTcF = QT interval corrected for heart rate using Fridericia's formula.

Notable ECG abnormalities are derived as described in Table 11 and defined for the following periods:

- Day of first study drug intake (up to 24 hours after first study drug intake).
- During TP1: up to Month 6 for subjects who complete TP1 on treatment and up to EOT for subjects who discontinue study treatment during TP1.
- During TP2: up to EOT.
- Treatment-emergent (combining TP1 and TP2 data): up to EOT + 180 days.

Values and changes derived above will be used to characterize abnormalities.

8.6.2.3 Morphological ECG abnormalities/findings (12-lead ECG)

Morphological ECG findings are defined for:

- Day of first study drug intake (up to 24 hours after first study drug intake).
- During TP1: up to Month 6 for subjects who complete TP1 on treatment and up to EOT for subjects who discontinue study treatment during TP1.

- During TP2: up to EOT.
- Treatment-emergent (combining TP1 and TP2 data): up to EOT + 180 days.

Due to the automatic transfer of data from the hospital to the vendor all date and time information should be complete. In the unlikely event of missing date and time, the missing information is imputed in the same way as the date and time information for TEAEs.

8.6.2.4 Holter ECG

Due to the HR-lowering effect of cenerimod on the first day of study drug intake the baseline Holter value and all other post-baseline values are derived dependent on the time of the first study drug intake. Baseline is defined as the average HR prior to first study drug intake.

Hourly averages of the HR after baseline are also calculated based on the time of the first study drug intake.

Example:

If the start time of first study drug intake is 8:22:00 am, the mean HR in the interval [7:22:00 am (or start of recording); 8:21:59 am] is considered as the baseline value and the mean HR in the interval [8:22:00 am; 9:21:59 am] is considered as the first hourly interval. The mean HR is calculated for 24 intervals (if data available).

For each Holter ECG, a cardiologist will provide an overall interpretation (Normal/Abnormal) and will describe potential findings.

Each finding reported for the Holter ECG performed on the day of first study drug intake is considered to be treatment-emergent (up to 24 hours after the start of recording).

Absolute changes of the mean hourly HR are defined as follows:

Changes of the mean hourly HR = mean hourly HR at hour X – mean hourly HR at baseline

8.6.3 Analysis

8.6.3.1 12-lead ECG

All ECG outputs will be summarized using the SAF and SAF-TP2.

Standard summary tables will be produced, by time point, for any ECG parameter provided by the vendor on the day of first study drug intake by treatment group. A similar summary table will be produced by study visit, for TP1, for TP2 and for TP1 and TP2 combined. Figures over time will be produced to support the summary tables.

The incidence of ECG outliers / notable ECG abnormalities and morphological ECG findings will be summarized for the periods defined above.

A subject will be counted only once in the most severe category of a given parameter. An abnormality is only counted as treatment-emergent if the criterion itself and all more severe criterion for the same parameter were not already present at baseline.

Percentages will be based on the number of subjects at risk, i.e., those not meeting the criterion or a more severe criterion for the same parameter at baseline (or having a missing baseline value) and having at least one post-baseline value for a given parameter. For criteria that are based on an increase from baseline, subjects with a missing baseline value are not included in the number of subjects at risk.

For QTcB and QTcF, a shift table from baseline to worst value post-baseline will be produced based on the abnormalities.

The incidence of ECG outliers/notable ECG abnormalities and morphological ECG findings will be summarized for TP2 as well. Outputs will be displayed in the same way as described above, based on 6 treatment groups using the SAF-TP2.

ECG data (parameters and findings) will be listed by treatment group, subject and visit using the SAF.

All post-treatment notable abnormalities will be flagged and qualitative abnormalities (as transferred by the ECG central reader) will be listed using the SAF.

8.6.3.2 Holter ECG

Standard summary tables of the mean hourly HR observed values and changes from baseline will be produced, by time point and treatment group, for the day of first study drug intake. Figures over time will support the summary tables.

Holter ECG findings (with codes from [001] to [019] in SDTM CO domain) will be summarized by treatment group. When mentioned in the finding, number of episodes will not be included in the finding verbatim for the summary table but will be displayed as collected in the listing.

Holter ECG data will be listed by treatment group, subject and visit using the SAF. A listing of all Holter ECG abnormalities will also be provided.

8.7 Vital signs and body weight

Blood pressure data are collected on the Vital Signs eCRF page.

Weight is collected on the Body Weight eCRF page.

The HR is only collected in the ECG data and therefore not analyzed in this section.

A time window approach will be applied to the vital signs / weight data [as defined in Section 5.4.4].

8.7.1 Blood pressure

8.7.1.1 Measurements

For SBP and DBP two measurements will be performed pre-dose at every visit (except FU2, FU3, FU3a, and FU3b).

For the randomization visit and the re-initiation visit, where the subject stays in the hospital for an extended period of time, single hourly post-dose measurements will be performed.

8.7.1.2 Blood pressure over time

8.7.1.2.1 Variables

Absolute change of blood pressure is derived on the day of first study drug intake, on the day of re-initiation and generally from the last valid assessment prior to first study drug intake to each pre-dose assessment at any visit during the conduct of the study.

Absolute changes are derived for SBP and DBP separately, based on measurements at each (hourly) visit. In the event of two available measurements the mean of those two measurements is computed.

Intra-day change is defined for the day of first study drug intake and the day of re-initiation, by hour:

Hourly intra-day change = Blood pressure value at hourly post-dose assessment – mean blood pressure value at pre-dose assessment

The mean blood pressure value at the pre-dose assessment must be assessed on the day of first study drug intake / day of re-initiation, otherwise it is considered to be missing.

Some subjects might stay longer in hospital than the expected 6 hours. Intra-day changes are also calculated for assessments performed later than 6 hours after first study drug intake.

Pre-dose assessments are identified by date and time. Blood pressure is assessed twice at each pre-dose visit and the mean of those two measurements is used to calculate the change. In the event that only one measurement is performed at any (hourly) visit, this single measurement is used for analysis instead of the mean.

Changes compared to the derived mean baseline value are defined as:

Change = Mean blood pressure value at post-baseline visit (pre-dose) – derived mean baseline value

The derived mean baseline value is the mean of the last two blood pressure values measured on the same day before first study drug intake (by date and time). In the event of missing pre-dose data on the day of first study drug intake, the mean of the closest measurements prior to first study drug intake (e.g., at Screening) is used.

Changes from TP2 baseline will be derived in the same way.

All data independent of the position (sitting, standing, supine) and location (right arm, left arm) are included in the derivation.

8.7.1.2.2 Analysis

Blood pressure parameters will be summarized using the SAF (for day of first study drug intake, for TP1 and for TP1+TP2 combined) and using the SAF-TP2 (for TP2) by time point / visit and treatment group [as defined in Section 5.4.3].

Blood pressure data will be listed using the SAF.

8.7.1.3 Notable blood pressure abnormalities

8.7.1.3.1 Variables

For SBP and DBP, the occurrence of notable abnormalities (up to EOT + 180 days) is assessed according to the criteria defined in Table 12. Values and changes derived above will be used to characterize abnormalities.

Table 12 Notable abnormalities in blood pressure

Analysis parameter	Analysis criterion
SBP (mmHg)	Value ≤ 90 and decrease ≥ 20 from baseline
	Value ≥140 and increase ≥ 20 from baseline
	Value ≥ 160
DBP (mmHg)	Value ≤ 50 and decrease ≥ 15 from baseline
	Value ≥ 90 and increase ≥ 15 from baseline
	Value ≥ 100

DBP = diastolic blood pressure; SBP = systolic blood pressure.

Abnormalities are defined for:

- Treatment-emergent on day of first study drug intake: up to 24 hours after first study drug intake.
- During TP1: up to Month 6 for subjects who complete TP1 on treatment and up to EOT for subjects who discontinue study treatment during TP1.
- During TP2: up to EOT.
- Treatment-emergent (combining TP1 and TP2 data): up to EOT + 180 days.

8.7.1.3.2 Analysis

Treatment-emergent notable blood pressure abnormalities will be summarized descriptively using the SAF (treatment-emergent on day of first study drug intake, during TP1, and during TP1 and TP2) and the SAF-TP2 (during TP2).

An abnormality is only counted as treatment-emergent if the criterion was not already present at baseline.

Percentages will be based on the number of subjects at risk, i.e., those not meeting the criterion at baseline (or having a missing baseline value) and having at least one post-baseline value for a given parameter. For criteria that are based on the change from baseline, subjects with a missing baseline value are not included in the number of subjects at risk.

8.7.2 Body weight

8.7.2.1 Variables

Weight is summarized over time and changes are derived as follows:

Change = Weight at post-baseline visit – baseline weight.

Changes are also derived based on TP2 baseline.

8.7.2.2 Analysis

Absolute values and changes from baseline up to EOS will be summarized using the SAF. Absolute values and changes from baseline during TP1 will be summarized using the SAF and during TP2 using the SAF-TP2.

Weight data will be listed using the SAF.

8.8 Echocardiography (sub-study)

Standard 2D/Doppler data are collected for all subjects at Screening and for approximately 175 subjects in the study at Month 6 or premature EOT visit.

8.8.1 Measurements

Cardiac morphology and function including regional wall abnormalities, aortic valve morphology and function, mitral valve morphology and function, and left ventricular ejection fraction are collected in this study.

Abnormalities from Screening to Month 6 are assessed by Standard 2D/Doppler echocardiography.

Abnormalities and cardiac data (as defined above) will be received by a vendor.

A time window approach will be applied [as defined in Section 5.4.4].

8.8.2 Variables

The change in left ventricular ejection fraction is computed as:

Change in left ventricular ejection fraction (%) = Left ventricular ejection fraction (%) at Month 6 or premature EOT visit – Left ventricular ejection fraction (%) at Screening.

8.8.3 Analysis

Standard summary tables will be produced using the ECS, by treatment group, for the change in left ventricular ejection fraction from Screening to Month 6 or premature EOT visit.

Abnormalities will be summarized descriptively using the ECS.

Echocardiography data will be listed using the SAF.

8.9 Biomarker endpoints

The following biomarkers are assessed:

- total lymphocyte count
- anti-cardiolipin antibodies (IgA, IgG, IgM)
- Anti-nuclear antibodies
- anti-dsDNA antibodies
- anti-Smith antibodies
- C3 and C4 complement

The following biomarkers will be included in summaries (numerically).

- Anti-nuclear antibodies
- anti-dsDNA antibodies
- anti-Smith antibodies
- C3 and C4 complement

Qualitative assessments (e.g., Normal/Abnormal) will only be listed.

A time window approach will be applied [as defined in Section 5.4.4].

8.9.1 Variables

The absolute change and percent change from baseline in biomarker parameters at each post-baseline analysis visit up to EOS is calculated as follows:

- Change in biomarker parameters = Biomarker value at Visit X – Biomarker value at baseline

- Percent change in biomarker parameters = (Biomarker value at Visit X − Biomarker value at baseline) / Biomarker value at baseline × 100

Baseline is defined as the last valid biomarker value prior to first study drug intake, by time and date.

8.9.2 Analysis

Biomarker data will be analyzed using the FAS and data up to the EOS visit.

For biomarkers standard summary statistics for absolute values, absolute change and percent change from baseline will be presented, by visit and treatment group.

Summary statistics of percentage changes will be derived from the geometric mean of the ratio to baseline. Because geometric mean of data is equivalent to exp(mean of log-transformed data), the geometric mean of the ratio to baseline is equivalent to exp(mean of log[post-baseline/baseline]), equivalent to exp(mean of (log[post-baseline] – log[baseline])). Geometric mean of the ratio to baseline will be transformed into a percentage change by using the transformation x – > ((x-1) × 100).

The CV of the geometric mean will be derived as:

$$100 \times \sqrt{\exp\left(\left(SD_{log}\right)^2\right) - 1}$$

Note that anti-cardiolipin antibodies are only collected at baseline and therefore only the baseline summaries will be presented for this parameter.

Biomarkers will be listed using the FAS.

9 GENERAL STATISTICAL METHODOLOGY

9.1 General rules for data presentations

Unless otherwise specified, data will be summarized using appropriate descriptive statistics:

- For continuous variables: number of non-missing observations, mean, standard deviation, minimum, first quartile, median, third quartile and maximum.

  Results will be displayed in the format of the eCRF for median, percentiles, minimum and maximum values. They will be displayed with one additional digit for the mean and the 95% CIs. The standard deviation will be displayed with one more digit than the mean.

- For dichotomous or categorical variables: number of non-missing observations, and frequency with percentage per category. Denominators for percentages are the number of subjects in the pertinent analysis set and treatment group, unless otherwise specified.

- For time-to-event variables: number of events, number at risk, number of censored observations and Kaplan-Meier estimates of the survival function.

In listings, subject number is presented as "SUBJID/SEX/AGE".

A percentage change from baseline is defined as the absolute change from baseline divided by the baseline value (if the baseline value is > 0) and then multiplied by 100. In the event of baseline and post-baseline value both equal to 0, the ratio to baseline will be set to 1 (i.e., the percent change from baseline will be set to 0%). If baseline is equal to 0 and post-baseline value greater than 0 (infinite ratio) or if baseline greater than 0 and post-baseline equal to 0 (log[ratio] = minus infinity), the percent change will be missing.

10 INTERIM ANALYSES

No interim analyses are planned according to protocol.

11 REFERENCES

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12 APPENDICES

12.1 Visit and assessment schedule

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

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

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

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

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

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

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

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

(1) Prior to Randomization, the following central laboratory results must be available to confirm eligibility: ANA, anti-dsDNA, anti-HAV IgM, Hepatitis B surface antigen, Hepatitis C antibodies (anti-HCV IgG or IgM), anti-HEV IgM and/or IgG, HEV-RNA PCR (as needed), HIV1 and HIV2, varicella-zoster virus IgM antibody, urine protein-to-creatinine ratio, ALT/AST/TBIL and pregnancy test (if applicable).
(2) A complete physical examination (i.e., inspection, percussion, palpation, and auscultation) will only be performed at Visits 1, 2, 3, 5, 8, 11, 14, and 15. For all other visits, a symptom-driven abbreviated physical examination will be performed in order to capture assessments needed for the SLEDAI-2K, the PGA, the BILAG, and the SFI.
(3) Height only at Screening. Body weight should be measured as part of BILAG assessment at each applicable visit and recorded in the source documentation. If clinically relevant, body weight collected outside Screening, EOT and EOS visits may be reported as an Unscheduled assessment.
(4) Echocardiography will be performed at Visit 1 (Screening) preferably within 30 days prior to Randomization for all subjects and at Visit 8 (Month 6) in approximately 175 subjects, as part of the ancillary study. In the event of premature study treatment discontinuation during TP1 (i.e., before Visit 8), echocardiography will be performed at pEOT visit and will not be required at Visit 8.
(5) A chest X-ray that has been performed within 6 months prior to Screening can be used (in this case, there is no need to repeat the chest X-ray at Screening).
(6) At each pre-dose assessment, SBP/DBP measurements will be performed twice in the supine position.
(7) On Day 1 and at Re-initiation visit, SBP/DBP assessment and 12-lead ECG will be done pre-dose and hourly until 6 h post-dose; after 6 h, subjects may be discharged if they meet the discharge criteria, otherwise SBP/DBP assessments and 12-lead ECG will be performed hourly until discharge criteria are met. If discharge criteria are not met after 12 h, the subject must be permanently discontinued. At all other visits, only pre-dose SBP/DBP assessments and 12-lead ECG will be performed.

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

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

12.2 Definitions of AEs of special interest

The definitions for AESIs are based on a systematic approach using SMQs. The additional relevant term can be added to the search or deleted appropriately providing the rationale for the change. The current proposal is based on MedDRA version 25.0. The following safety areas are addressed by the pre-defined AESIs. Note that all SMQs are considered as broad searches (i.e., including broad and narrow terms) unless noted otherwise.

Narratives will be written for all SAEs, pregnancy and death events reported to Global Drug Safety, including those not meeting the definition of AESIs.

- **Effect on HR and rhythm AESI**

Effect on HR and rhythm AESI are identified by the PTs in the following SMQ: **Bradyarrhythmias (incl conduction defects and disorders of sinus node function) (SMQ).** Note that this SMQ only has narrow scope defined.

In addition, to the PTs included in Bradyarrhythmias (including conduction defects and disorders of sinus node function [SMQ]), the following PTs will be added to the search for AEs addressing effects on HR and rhythm:

"BRADYCARDIA", "ELECTROCARDIOGRAM RR INTERVAL PROLONGED", "HEART RATE DECREASED", "CHRONOTROPIC INCOMPETENCE", "PRESYNCOPE", "SYNCOPE", "LOSS OF CONSCIOUSNESS", and "CENTRAL BRADYCARDIA".

AESI Narratives will be written for AEs of confirmed symptomatic events on HR and rhythm (e.g., symptomatic bradycardia, etc.). Narratives will be written for AV block 2nd and 3rd degree, but not for AV block 1st degree.

- **Hypotension AESI**

The following PTs will be added to the search for AEs addressing hypotension: "BLOOD PRESSURE DECREASED", "BLOOD PRESSURE DIASTOLIC DECREASED", "BLOOD PRESSURE ORTHOSTATIC DECREASED", "BLOOD PRESSURE SYSTOLIC DECREASED", "DIASTOLIC HYPOTENSION", "MEAN ARTERIAL PRESSURE DECREASED", "ORTHOSTATIC HYPOTENSION", "PROCEDURAL HYPOTENSION", "HYPOTENSION", "CIRCULATORY COLLAPSE", "BLOOD PRESSURE AMBULATORY DECREASED", "BLOOD PRESSURE IMMEASURABLE", "BLOOD PRESSURE SYSTOLIC INSPIRATORY DECREASED", "CT HYPOTENSION COMPLEX", "DISTRIBUTIVE SHOCK", "PROCEDURAL SHOCK", "SHOCK", "SHOCK HAEMORRHAGIC", and "SHOCK SYMPTOM", "HYPOTENSIVE CRISIS", "POST PROCEDURAL HYPOTENSION", "HYPOVOLAEMIC SHOCK", "CARDIOGENIC SHOCK", "PERIPHERAL CIRCULATORY FAILURE".

AESI Narratives will be written for confirmed symptomatic hypotension events.

- **Cardiovascular AESI**

Cardiovascular AESI are identified by any PT in the following SMQs: **Ischaemic heart disease (SMQ, narrow scope)** or **Torsade de pointes/QT prolongation (SMQ, broad scope)** or **Cardiac failure (SMQ, narrow scope).**

AESI Narratives will be written for these AESIs only if reported as SAE.

- **Hypertension AESI**

Hypertension AESIs are identified by the PTs in the following SMQ: **Hypertension (SMQ, narrow scope).**

AESI Narratives will be written for these AESIs only if reported as SAE.

- **Hepatobiliary disorders / Liver enzyme abnormality AESI**

Hepatobiliary disorders/ Liver enzyme abnormality AESIs are identified by the PTs in the following SMQ: **Drug related hepatic disorders - comprehensive search (SMQ).**

AESI Narratives will be written for lab abnormalities or AEs of ALT or AST >= 3 × ULN. No narrative will be written for AEs declared without ALT or AST being >= 3 × ULN.

- **Pulmonary AESI**

These AEs are identified by the PTs the in the following SMQs: **Asthma/bronchospasm (SMQ)** or **Interstitial lung disease (SMQ).**

The PTs “DYSPNOEA AT REST”, “DYSPNOEA” and “DYSPNOEA EXERTIONAL” which are not included in the above-mentioned SMQs are added to the search.

SMQs related to respiratory system do not cover all the PTs on investigation (i.e., AEs based on pulmonary function test or chest X-ray or computerized tomography scan). Therefore, the PT from the MedDRA SOC ‘Investigations’ identified by the following HLGT are added to the search: **‘Respiratory and pulmonary investigations (excl blood gases)’ (HLGT)** with the exception of the following PTs: “CAPNOGRAM NORMAL”, “END-TIDAL CO2 NORMAL”, “EXPIRATORY RESERVE VOLUME NORMAL”, “FORCED EXPIRATORY VOLUME NORMAL”, “FORCED VITAL CAPACITY NORMAL”, “FUNCTIONAL RESIDUAL CAPACITY NORMAL”, “INSPIRATORY CAPACITY NORMAL”, “MAXIMAL VOLUNTARY VENTILATION NORMAL”, “PEAK EXPIRATORY FLOW RATE NORMAL”, “PULMONARY FUNCTION CHALLENGE TEST NORMAL”, “PULMONARY FUNCTION TEST NORMAL”, “RHINOMANOMETRY NORMAL”, “SPIROMETRY NORMAL”, “TOTAL LUNG CAPACITY NORMAL”, “VITAL CAPACITY NORMAL”.

AESI Narratives will be written for Pulmonary Functional Tests meeting the study treatment discontinuation criteria defined in protocol section 5.1.8.3.

- **Macular edema AESI**

Macular edema AESI are identified by the following PTs: "MACULAR OEDEMA", "MACULAR HOLE", "MACULAR PSEUDOHOLE", "MACULAR RUPTURE", "MACULAR THICKENING", "MACULAR CYST", "RETINAL OEDEMA", "DIABETIC RETINAL OEDEMA", "CYSTOID MACULAR OEDEMA", "PAPILLOEDEMA", and "PSEUDOPAPILLOEDEMA".

AESI Narratives will be written for cases reviewed by the Ophthalmology Safety Board.

- **Eye disorder AESI**

Eye disorder AESI are identified by the PTs in the following SMQ: **Retinal disorders (SMQ, narrow scope)**.

AESI Narratives will be written for cases reviewed by the Ophthalmology Safety Board.

- **Infection AESI**

Infection AESI are identified by the PTs in the following SMQ: **Opportunistic infection (SMQ)**.

AESI Narratives will be written for all these AESIs, except for COVID-19 cases that are not reported as SAE.

- **Skin malignancy AESI**

Skin malignancy AESI are identified by the PTs in the following SMQs: **Skin neoplasms, malignant and unspecified (SMQ)** or **Skin premalignant disorders (SMQ) (broad and narrow scope, including all sub SMQs).**

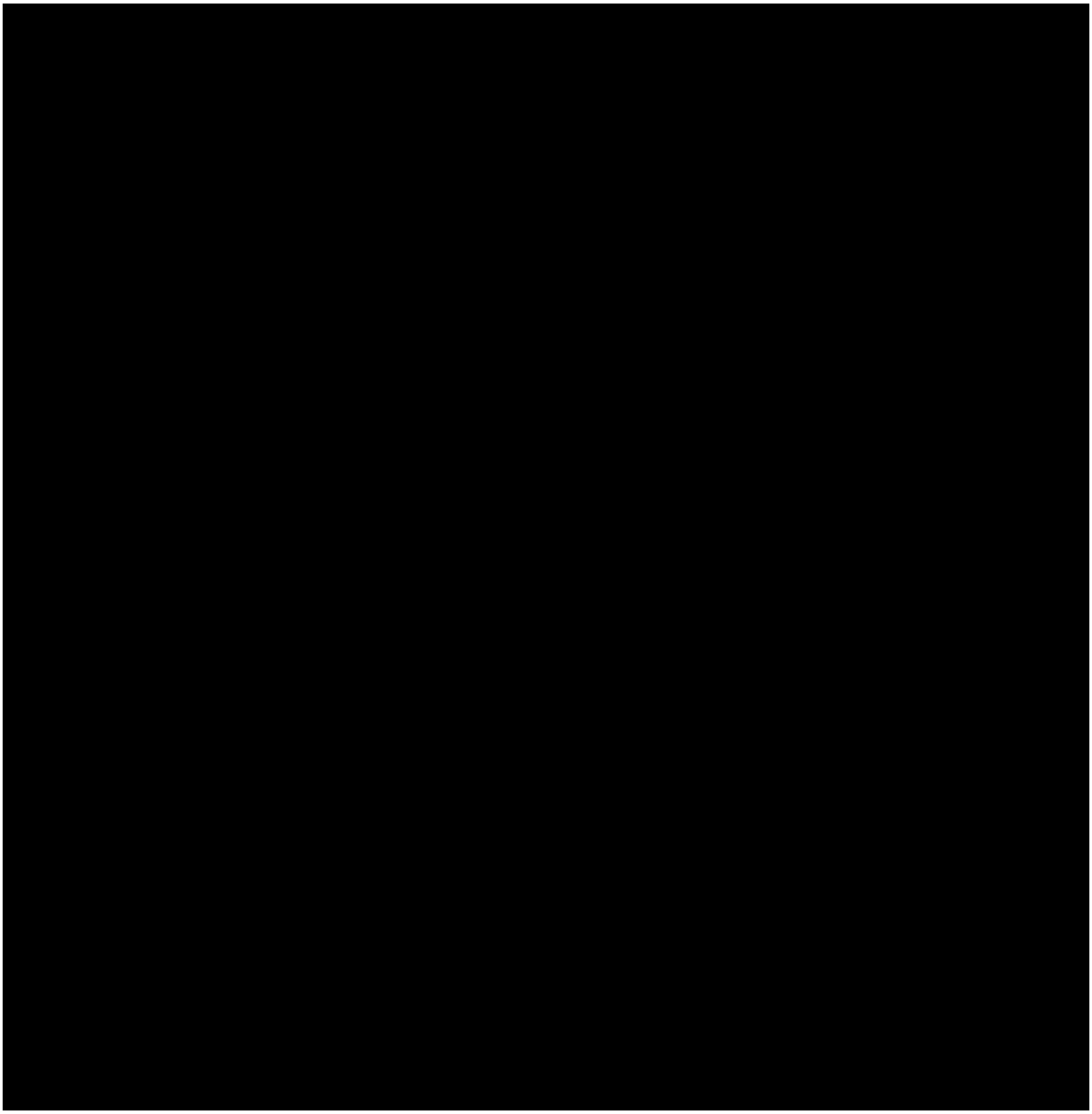
AESI Narratives will be written for all these AESIs.

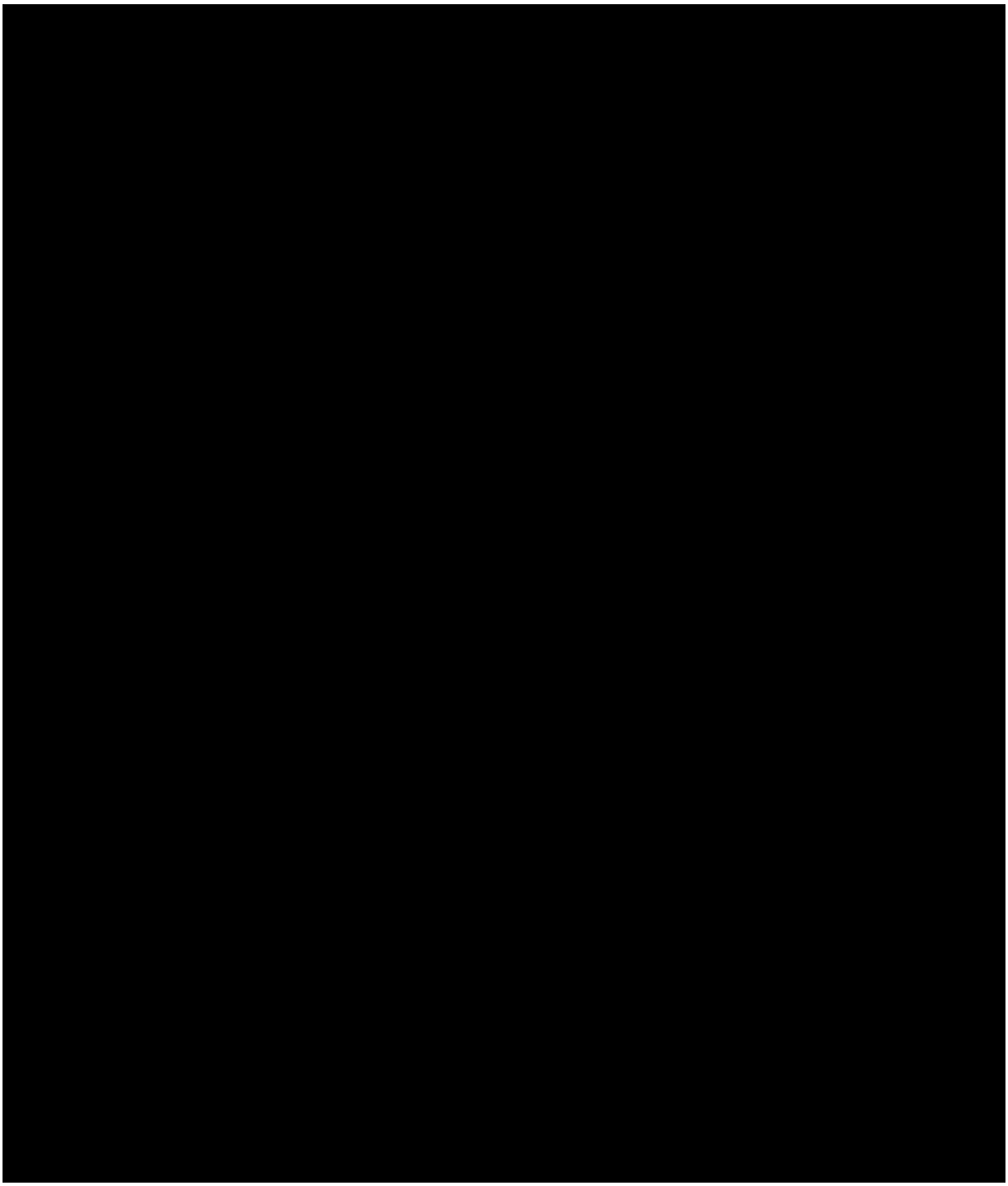
- **Non-skin malignancy AESI**

Non-skin malignancy AESI are identified by the PTs in the following SMQs: **Malignant tumours (SMQ)** or **Malignant lymphomas (SMQ; Narrow scope)** excluding the PTs included in the 'Skin malignancy AESI'.

AESI Narratives will be written for all these AESIs.

12.3 SF-36v2™





Computing domain scores

[redacted]

Computing normalized domain scores

[redacted]

[redacted]

Computing PCS and MCS measures

[redacted]

Missing data

[redacted]

12.4 FACIT-Fatigue scoring manual

FACIT-Fatigue Subscale Scoring Guidelines (Version 4) – Page 1

[redacted]

*For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on-line at www.facit.org.

[redacted]

12.5 Revision history

Version Date	Version	Implemented Change(s)
5-Aug-2019	1.0	New
27-Aug-2020	2.0	• Section 2.1: added paragraph on the echocardiography ancillary study. • Section 3.1.1: the final ICH E9 addendum was not available when version 1 of this SAP was prepared. The draft ICH E9 addendum did not include the "treatment condition of interest" attribute. This was now added in this SAP. • Section 4.1: clarified definition of 'treatment received' and updated analysis set labels to remove 'TP1' as these analysis sets are also used for analyses that combine data from TP1 and TP2. • Section 5.4.3: updated treatment groups for exploratory analyses of TP2 data and TP1 + TP2 data combined. Clarified treatment groups used in listings. • Section 6.1: updated to account for re-screening which was not allowed in previous protocol version. • Section 6.2.2: removed summary table of eligibility criteria. • Sections 6.3, 6.4, 6.5, 6.6, 6.9: data will be presented separately during TP1, during TP2 and during TP1 + TP2. • Section 6.6: added listing for subjects unblinded during the study; added summaries of DVs related to COVID-19 pandemic. • Section 6.7.2: clarified that analysis sets will be summarized separately by randomized group and treatment received. Separate tables for re-randomized groups added. Added tables for reasons of exclusion. • Section 6.8.1.2: added demographics by sex table. • Section 6.8.2.2: clarified that stratification factors will be presented as shift table. • Section 6.8.6: added summaries for concomitant at baseline therapies; clarified definition of SLE therapies; clarified date imputation; added summary of changes in background medications. • Section 7.2.3: added patterns of missingness table and figure showing mean change from baseline by study completers and withdrawals. • Section 7.2.5: added further details for MMRM specification. • Section 7.2.7.2, 7.3.1.7: clarified subgroup analyses (separate models per subgroup). • Sections 7.3.1.3, 7.3.2.3: added patterns of missingness table. • Section 7.3.1.5: added further details for GLMM specification. • Sections 7.3.1.6.2, 7.3.1.6.3, 7.3.2.6.2, 7.3.2.6.3: added additional sensitivity analyses. • Sections 7.5.2.2, 7.5.3.2, 7.5.4.2, 7.5.5.2, 7.5.6.2, 7.5.8.2, 7.5.9.2: clarified that only re-randomized groups are included in models of TP2 data.

		• Section 7.5.10: added more details for derivation of monthly prednisone equivalent dose. • Section 8: safety events will be presented as occurring during TP1, occurring during TP2 and treatment-emergent. • Section 8.2.2: defined 3 overview tables instead of only one (AEs with onset during TP1, AEs with onset during TP2, treatment-emergent AEs) and replaced several subsections by bullet list of outputs. • Sections 8.4.3, 8.6.3, 8.7.1.3.2: clarified definition of emergent events. • Section 11: removed these exploratory analyses which will not be performed for CSR. • Appendix 12: removed laboratory abnormalities table and refer to protocol appendix instead. • Appendix 12.4: added FACIT-Fatigue scoring manual. • Other minor clarifications and editorial updates.
09-Sep-2021	3.0	• Section 2 (Study design): Updated following protocol amendment (protocol version 4.0): - Sample size reduced from 500 to 325 - Planned end of TP2 will be 12 months after initial randomization, for all subjects - Describe Month-6 and Month-12 analyses milestones • Section 4.1.4 (Per-Protocol Set): criteria for exclusion from the PP set are detailed in an excel file, to facilitate the reading • Section 4.2 (Usage of analysis sets): Clarify that in the event of accidental intake of a treatment other than the randomized treatment occurring during TP2, actual treatment group for TP1 only will be the randomized treatment • Section 5.1 (Study dates) and section 6.2 (Eligibility criteria): Updated to include possibility for re-screening introduced in a protocol amendment • Section 5.4.3 (Treatment groups for analysis according to treatment period): Labels for treatment groups updated after team review during dry-run 1 • Section 5.4.3 (Treatment groups for analysis according to treatment period): Treatment group of those randomized to cenerimod 4mg during TP1 and not re-randomized will be displayed in a selection of outputs (disposition, treatment-emergent safety events) • Section 6.1: added description of screening failures related to COVID-19 pandemic. • Section 6.2 (Eligibility criteria): Added summary of eligibility criteria for screen failures not eligible as per inclusion/exclusion criteria • Section 6.3 (Subject disposition): Disposition updated following dry-run 1 comments • Section 6.4: added description of study treatment discontinuation related to COVID-19 pandemic.

		• Section 6.5: added description of study discontinuation related to COVID-19 pandemic. • Section 6.8.6 (Previous and concomitant therapies): Description of background SLE therapies by ATC and PT was replaced by a description by categories mentioned in the protocol and PT • Section 6.9.2 (Compliance): Clarifications on derivation of compliance when the kit is not returned or was replaced • Section 7 (Efficacy analyses): subject random effect was removed from all models • Number of replicated for multiple imputation was reduced from 500 to 100 for all analyses using MI • Section 7.2.6.9 (Dose-response analysis): MCP-Mod analyses to be performed were clarified and piece of code added • Section 7.4.5 (Time to first severe flare up to Month 6), section 7.4.6 (Time to first flare up to Month 6): Log-rank test was removed • Section 7.5.1 (Sustained mSLEDAI-2K response): Added the definition of subjects with enough assessments to be assessed for this endpoint • Section 7.5.10 (Change from baseline to each post-baseline assessment up to Month 12 in prednisone or equivalent dose): Clarification of the analysis windows: If a subject has a visit recorded after Month 6 but the Month 6 visit was not done, Month 6 visit will be replaced by Day 180. • Section 7.6.1 (FACIT-Fatigue): Month-3 analysis timepoint was added following protocol amendment (protocol version 4.0) • Section 7.6.4 (SF 36v2™): The health transition score will only be described at Month 12, as it rates the current state compared to one year before • Section 7.6.5 (Lupus QoL): Scoring details were described as per scoring manual • Section 7.6.6 (mucocutaneous and musculoskeletal score): The sum of the mucocutaneous and musculoskeletal score will also be described • Section 8.5 (Spirometry): Formula for percent change from baseline expressed as percent of predicted baseline for FEV1 and FVC was corrected • Section 8.5 (Spirometry): Geometric mean and CV for percent change from Baseline were added following dry-run 1 review • Section 8.8 (Echocardiography sub-study): Sample size increased from 125 to 175 following protocol amendment (protocol version 4.0) • Section 8.8 (Echocardiography sub-study): All abnormalities will be described, not only clinically relevant ones • Section 8.9 (Biomarkers): List of selected biomarkers (quantitative variables) to be described was added. All other biomarkers (qualitative variables) will only be listed • Section 8.9 (Biomarkers): Derivation of geometric mean for percent change from baseline was clarified

		• Section 9.1 (General rules for data presentations): Derivation of percentage change from baseline was added • Section 12.1 (Visit and assessment schedule): Updated following protocol amendment (protocol version 4.0) • Section 12.2 (Definitions of AEs of special interest): AESI list was updated following the last criteria for research provided by safety department, based on the last version of MedDRA used (v24.0) + AESIs for which narratives will be written was added
21-Mar-2022	4.0	Updates as per protocol Version 5 (protocol amendment 4): • Follow-up extended from 4 months to 6 months, with two new FU visits taking place (FU3a and FU3b): – Section 2.1 (Study design) – Section 2.3 (Study periods) – Section 8.4 (Laboratory tests) – Section 8.5 (Spirometry) – Section 8.7.1 (Blood pressure) – Section 12.1 (Visits and assessment schedule) • Month-12 analysis to be performed at last EOT (instead of EOS). The Final EOS analysis will take place at EOS. – Section 2.1 (Study design) • Minor wording updates – Section 4.2 (Usage of analysis sets) – Section 5.1 (Study dates) Added a rule in Section 5.1 (Study dates) to handle missing EOT dates in the eCRF due to the start of the conflict in Ukraine.
27-Sep-2022	5.0	• Update of the 'treatment-emergent' period (applicable for AEs, abnormalities, findings, etc.) following evidence for longer half-life for cenerimod (longer than the known half-life until then). • Section 6.4.1 (Study treatment discontinuation): wording update which should have been corrected in previous version (following protocol v4.0 Planned end of TP2 will be 12 months after initial randomization, for all subjects). • Section 6.6 (Protocol Deviations): Added a table of PDs related to the conflict in Ukraine + flag in listing. • Section 8.6.3 (Holter ECG): Remove number of episodes from the summary table of findings, as it is not relevant for summary and makes the table uninterpretable. • Section 12.2 (Definition of AESI): Updated as per upgraded MedDRA version (v25.0).