Integrated Analysis Plan

Study Number:	MS200569_0003
Clinical Study Protocol Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Dose-Ranging, Parallel and Adaptive Study to Evaluate the Efficacy and Safety of Enpatoran in Systemic Lupus Erythematosus and in Cutaneous Lupus Erythematosus (Subacute Cutaneous Lupus Erythematosus and/or Discoid Lupus Erythematosus) Participants Receiving Standard of Care
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Integrated Analysis Plan Reviewers:	PPD

Approval Page

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A Phase 2, Randomized, Double-Blind, Placebo-Controlled Dose-Ranging, Parallel and Adaptive Study to Evaluate the Efficacy and Safety of Enpatoran in Systemic Lupus Erythematosus and in Cutaneous Lupus Erythematosus (Subacute Cutaneous Lupus Erythematosus and/or Discoid Lupus Erythematosus) Participants Receiving Standard of Care

Approval of the IAP by all Merck Data Analysis Responsible has to be documented within EDMS via eSignature. With the approval, the Merck responsible for each of the analysis also takes responsibility that all reviewers' comments are addressed adequately.

By using eSignature, the signature will appear at the end of the document.

1 Table of Contents

2 List of Abbreviations and Definition of Terms

ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical classification
BICLA	BILAG-based Combined Lupus Assessment
BLQ	Below lower Limit of Quantification
BSA	Body Surface Area
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CS	Corticosteroids
C-SSRS	Columbia-Suicide Severity Rating Scale
eCRF	electronic Case Report Form
CLA-IGA	Cutaneous Lupus Activity Investigator's Global Assessment
CRI-7	CLASI-A Responder Index-7
CSR	Clinical Study Report
Ctrough	Concentration Observed at the End of Dosing Interval Immediately Before Next Dosing
CV%	Coefficient of Variation
EAC	Endpoint Adjudication Committee
ECG	Electrocardiogram
FAS	Full Analysis Set
GeoCV	Geometric Mean
GeoMean	Geometric Coefficient of Variation
eGFR	Estimated Glomerular Filtration Rate
HTA	Health Technology Assessment
HR	Hazard Ratio
IAP	Integrated Analysis Plan
ICE	Intercurrent Event
ICH	International Conference on Harmonization

IDMC	External Independent Data Monitoring Committee
IPD	Important Protocol Deviation
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LFTs	Liver Function Tests
LLDAS	Lupus low disease activity state
LLOQ	Lower Limit of Quantification
LS	Least Squares
LSSD	Lupus Symptom Severity Diary
MAR	Missing at Random
Max	Maximum
MCMC	Markov Chain Monte Carlo
MCP-Mod	Multiple Comparison Procedure – Modeling
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MMRM	Mixed Model for Repeated Measures
MNAR	Missing Not At Random
CCI	[redacted]
NCA	Non-Compartmental Analysis
Nd	Not done
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NRS	Numeric Rating Scale
PD	Pharmacodynamics
PGA	Physician's Global Assessment
PGIC	Patient Global Impression of Change
PK	Pharmacokinetics
PKAS	Pharmacokinetic Analysis Set
PRO	Patient-Reported Outcome
PT	Preferred Term
CCI	[redacted]
SAE	Serious Adverse Event

SCR	Screening analysis set
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
CCI	[redacted]
SLICC	Systemic Lupus International Collaborating Clinics
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SRI	Systemic lupus erythematosus Responder Index
TEAE	Treatment-Emergent Adverse Event
WHO-DD	World Health Organization Drug Dictionary

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	18 July 2022	PPD	Not applicable
2.0	25 March 2024	PPD	Section 5: • CCI [redacted] • reviewed strategy to handle intercurrent events of estimands “Time to first moderate/severe BILAG flare from Day 1” and “Time to first SFI severe flare from Day 1” as per protocol V3. Section 6.3: updated text to stick with the interim IAP. Section 6.4: specified that all data collected in the database, including data after Week 16, will be included in the primary analysis of Cohort A, unless otherwise stated. CCI [redacted] Section 8.1: revised the definition of full analysis set. Section 8.2: Subgroup analysis Japanese vs Non-Japanese cancelled in Cohort A due to small sample size. Section 12: added summary of lupus standard of care medication during the on-treatment period. Section 13: removed the summary of the mean number of tablets ingested per day, and the total number of tablets ingested during the study. Section 14.1: added sensitivity analysis number 2 conducting MCP-Mod approach using MMRM to estimate parameters which are used in the MCP-Mod. Section 14.1.6: subgroup analyses will be conducted using a MMRM instead of an ANCOVA. CCI [redacted] Section 14.4.1: • added summarization of CLASI-A Responder Index-7 and CLASI-70. • Added analysis of CLASI-A erythema and scale/hypertrophy scores. • Added analysis of percent change in CLASI-A total score from Baseline to Week 24 using MCP-Mod approach in Cohort A.

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
			Section 14.4.6: added summary tables and replaced boxplots by line plots Section 14.4.7: added summary tables and replaced boxplots by line plots CCI [redacted] Section 15.3: eGFR is considered as gradable. Only high direction will be considered for monocytes. Section 15.5: added a summary of notable ECG values observed during the on-treatment period. Appendix 18.1: specified that TTP, evidence of hemolysis and Isolated Coombs's test will not be considered as missing if not available when deriving the hematological system. Appendix 18.2: added frequency conversions and updated derivation of corticosteroid dose by on-treatment visit, removed specific algorithm to impute start and end dates and referred to Section 9.10. Minor updates throughout the document to reflect changes made in protocol V3.
3.0	03 July 2024	PPD	Section 5: Reduced scope of primary analysis of Cohort A. CCI [redacted] Section 9.1: clarified that all adverse events and treatment exposure data will be used in the analysis for the primary analysis of Cohort A. Section 14.1: specified which analyses will be conducting during the primary analysis of Cohort A. Section 14.3: specified that secondary endpoints will be analyzed during the final analyses only. Section 14.3.1: only one model will be performed per cohort at final analyses including data until Week 24. Section 14.3.13: only one model will be performed per cohort at final analyses including data until Week 24. CCI [redacted] Section 14.4.1: specified which analyses will be performed for the primary analysis of Cohort A. Section 14.4.2: specified that analysis will be performed during the final analysis of Cohort A only. Section 14.4.6: updated analysis of MOS-sleep quantity subscale. Section 14.4.7: updated analysis of MOS-sleep quantity subscale. Section 15: specified which analyses will be performed for the primary analysis of Cohort A. Section 15.3: moved bicarbonate laboratory parameter from non-gradable to gradable and specified which analyses will be performed for the primary analysis of Cohort A.

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
			Section 15.5: corrected time window and specified which analyses will be performed for the primary analysis of Cohort A. Section 16.2: Specified that only IFNa parameter will be considered for cytokines. Removed CH50 from the analysis. Specified immune cells panels and immune cells parameters for which boxplots will be produced. Removed visuals per disease diagnosis within Cohort A.
4.0	13 December 2024	PPD	Section 9.7: updated time window for Week 24 and Week 26 safety follow-up visits. Section 9.11.2: • Clarified that the laboratory results from the serologic domain are disregarded when deriving the CCI clinical score. • Clarified that imputation at the item level is not performed if the questionnaire is not done. Section 9.11.3: clarified that imputation at the item level is not performed if the questionnaire is not done. CCI [redacted] Section 9.11.4: PGA comprises only one item. Hence, no imputation is done if the questionnaire is not done to be consistent with other questionnaires (where no imputation is performed when the questionnaires are not done like BILAG and CCI Section 14.3.6: added description of each SRI-4 component over time. Section 14.4.4: specified that the analysis will be performed in Cohort B participants with daily prednisone-equivalent dose ≥ 10 mg at Day 1. Section 15.1.1: Removed the overview of TEAEs in SLE participants from Cohort A and Cohort B combined. Section 15.3: Mean Corpuscular Hemoglobin is analyzed in the low direction only. Section 18.1.2: corrected serologic and hematologic domains.

4 Purpose of the Integrated Analysis Plan

The purpose of this IAP is to document technical and detailed specifications for the primary analysis of Cohort A and the final analysis of Cohorts A and B. An interim IAP describing the results of the interim analyses is provided as an appendix to this IAP. Results of the analyses described in this IAP will be included in the CSR. Additionally, the planned analyses identified in this IAP may be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

Additional analyses not covered by this IAP like, for instance, CCI [redacted] not pre-defined in the protocol or additional sub-group analyses planned for HTA submission, will be listed in the respective Data Analysis Responsibility form which is stored in the EDMS together with this IAP.

The IAP is based upon Section 9 (Statistical considerations) of the study protocol and is prepared in compliance with ICH E9. It describes analyses planned in the protocol except for PK/PD modeling activities which will be specified in a pharmacometrics analysis plan. Results from this analysis will be reported in a separate report. Details of the external independent data monitoring committee (IDMC) analyses for quarterly review of the participants' safety without formal statistical analysis are also provided in appendices.

The wording used in this IAP is chosen to best match the respective wording in the study protocol template, the Clinical Study Report (CSR) template, CDISC requirements and special requirements for table layouts. Therefore, the approach described below is used.

Generally, the term 'participant' will be used instead of 'subject' or 'patient'. However, in tables and listings the term 'subject' will be used to match CDISC requirements, except for in-text tables where 'participant' will be used to match the CSR and protocol templates. Similarly, the term 'study intervention' will be used in this document instead of 'treatment' to match protocol and CSR templates, however, tables and listings will use 'treatment' for brevity reasons. Exceptions from this rule are commonly used terms like "on-treatment", "treatment-emergent", "treatment policy", "subject-years", "by-subject", or names of eCRF pages like "Treatment Termination" page.

5 Objectives and Estimands

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Objectives	Estimand attributes	IAP Section	Analysis
Primary			
To evaluate the dose-response relationship of enpatoran in reducing disease activity based on CLASI-A	Endpoint: Percent change from baseline in CLASI-A at Week 16 Population: Participants with active SCLE, DLE or SLE with predominantly active lupus rash Note: Cohort A participants Treatment: Enpatoran vs placebo CCI [redacted] ▪ [redacted] ▪ [redacted] ▪ [redacted] Population-Level Summary: LS means (SE) as estimated by Mixed model with repeated measures (MMRM). The MCP-Mod procedure will be performed to evaluate the dose-response relationship.	14.1	Primary (Cohort A)

Objectives	Estimand attributes	IAP Section	Analysis
To evaluate the dose-response relationship of enpatoran in reducing disease activity based on BICLA response rate	Endpoint: BICLA response at Week 24 Population: Participants with active SLE Note: Cohort B participants Treatment: Enpatoran vs placebo CCI [redacted] Population-Level Summary: Responder rates and 95% CI. The MCP-Mod procedure will be performed to evaluate the dose-response relationship	14.2	Final
Secondary			
To evaluate the safety and tolerability of enpatoran compared to placebo	Endpoints: From Day 1 to the end of Safety Follow-up period • Occurrence of TEAEs, SAEs and AESI • Occurrence of abnormalities (Grade 3) in laboratory parameters • Occurrence of Clinically Important increases in QT Interval Corrected Using Fridericia's Formula (QTcF)	15	Primary Final
To evaluate the efficacy in disease control of enpatoran compared to placebo in lupus participants with active lupus rash	Endpoints: • Change from baseline in CLA-IGA at Week 16 and Week 24 • Change from baseline in Physician's Global Assessment of Cutaneous Lupus Disease Activity at Week 16 and 24	14.3.1 14.3.2	Final

Objectives	Estimand attributes	IAP Section	Analysis
	Population: Participants with active SCLE, DLE or SLE with active lupus rash Note: Cohort A participants OR Cohort B participants with CLASI-A ≥ 8 at Screening and confirmed at Day 1 CCI [redacted] Population-Level Summary: LS mean (SE) at each visit and treatment difference (95% CI) as estimated by MMRM		
To demonstrate the effect of enpatoran compared with placebo on achieving both BICLA response and clinically meaningful CS reduction in SLE participants on prednisone ≥ 10 mg at Day 1	Endpoint: BICLA response and clinically meaningful CS reduction, defined as reduction of daily prednisone-equivalent dose from ≥ 10 mg at Day 1 to ≤ 5 mg by the Week 12 visit and sustained through Week 24 Population: Participants with active SLE Note: Cohort B participants CCI [redacted] Population-Level Summary: same as BICLA response	14.3.3	Final
To evaluate the efficacy in disease control of enpatoran compared to placebo in lupus participants with predominantly active lupus rash	Endpoints: • Clinically meaningful CS reduction, defined as reduction of daily prednisone-equivalent dose from ≥ 10 mg at Day 1 to ≤ 5 mg by the Week 12 visit and sustained through Week 24 • Occurrence of CLA-IGA 0 or 1 at Week 16 and Week 24 Population: Participants with active SCLE, DLE or SLE with predominantly active lupus rash Note: Cohort A participants CCI [redacted] Population-Level Summary: number and proportion with 95% CI of participants achieving the respective response definition at Week 16 and Week 24	14.3.3	Final

Objectives	Estimand attributes	IAP Section	Analysis
To evaluate the efficacy in disease control of enpatoran compared to placebo in participants with active SLE	Endpoints: • Systemic lupus erythematosus Responder Index-4 (SRI-4) response at Week 24 • LLDAS attainment at Week 24 (Golder 2019) • Remission attainment at Week 24 (Vollenhoven 2021) • Clinically meaningful CS reduction, defined as reduction of daily prednisone-equivalent dose from ≥ 10 mg at Day 1 to ≤ 5 mg by the Week 12 visit and sustained through Week 24 Population: Participants with active SLE Note: Cohort B participants CCI [redacted] Population-Level Summary: Number and proportion with 95% CI of participants achieving the respective response definition at Week 12 and Week 24	14.3.6 14.3.7 14.3.8 14.3.3	Final
	Endpoint: • Change in the number of joints which are tender and swollen in 28-joint count from baseline at Week 24 Population: Participants with active SLE and at least 4 active joints at Baseline Note: Cohort B participants with at least 4 active joints at Baseline CCI [redacted] Population-Level Summary: Summary statistics at each visit	14.3.9	Final

Objectives	Estimand attributes	IAP Section	Analysis
	Endpoint: • Change from baseline in Physician's Global Assessment at Week 24 Population: Participants with active SLE Note: Cohort B participants CCI [redacted] Population-Level Summary: Summary statistics at each visit	14.3.10	Final
	Endpoints: • Time to first moderate/severe BILAG flare from Day 1 through Week 24 • Time to first SFI severe flare from Day 1 through Week 24 Population: Participants with active SLE Note: Cohort B participants CCI [redacted] Population-Level Summary: HR and CI from stratified Cox model, Kaplan-Meier estimates	14.3.11 14.3.12	Final
To evaluate the efficacy of enpatoran compared to placebo in patient-reported symptoms and functional status, in lupus participants with active lupus rash	Endpoints: • Change from Baseline in the Skindex-29+3 symptom domain score at Week 24 • Change from Baseline in the Skindex-29+3 Functioning and Emotion domain scores at Week 24. • Change from Baseline in the Skindex-29+3 lupus-specific domain scores at Week 24. • Change from Baseline in the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores at Week 24	14.3.13 14.3.14	Final

Objectives	Estimand attributes	IAP Section	Analysis
	Population: Participants with active SCLE, DLE or SLE with active lupus rash. Note: Cohort A participants OR Cohort B participants with CLASI-A ≥ 8. For FACIT-Fatigue: Cohort A participants. CCI [redacted] Population-Level Summary: Descriptive statistics at each visit and treatment difference at Week 24 as estimated by MMRM		
To evaluate the efficacy of enpatoran compared to placebo in patient-reported symptoms, in participants with active SLE	Endpoints: • Change from Baseline in the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores at Week 24 Population: Participants with active SLE Note: Cohort B participants CCI [redacted] Population-Level Summary: descriptive statistics at each visit and treatment difference at each study visit as estimated by MMRM	14.3.14	Final


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Cohort A: participants with active SCLE, DLE or SLE with predominantly active lupus rash, defined as patients with SCLE, DLE or SLE and a CLASI-A score at ≥ 8 at Screening and confirmed at Day 1.
Cohort B: SLE participants with active lupus rash, i.e., who have moderate to high systemic disease activity (BILAG ≥ 1A and/or 2B) with 1 or 2 of the following: CLASI-A ≥ 8 and/or CCI
MCP-Mod: Multiple Comparison Procedure – Modeling.

6 Overview of Planned Analyses

6.1 Analyses for Regular Safety External IDMC Meetings

The first external IDMC meeting will be held once 8 participants in Cohort A or Cohort B Part 1 have completed at least 12 weeks of treatment or discontinued permanently. Subsequent external IDMC meetings will occur every four months. Additional meetings may be scheduled by the IDMC.

Details of analyses for IDMC meetings are specified in a separate interim IAP provided in appendix 18.3.

CCI [redacted]

6.3 Interim Analyses for Cohort B Part 1

Two interim analyses will be conducted after 60 participants in Cohort B Part 1 have completed at least 12 weeks of treatment or discontinued the study intervention prematurely. Participants enrolled in Cohort B after those ~60 Cohort B Part 1 participants and prior to the data cut-off date (i.e., in Cohort B Part 2) will not be part of the analysis. The data cut-off applies to all the cohorts and studies used in the analyses, namely the ongoing Phase Ib study NCT04647708: participants from Cohort A and the ongoing Phase Ib study NCT04647708 randomized prior to the cut-off date will be included in the interim analyses.

These interim analyses aim at:

- The first interim analysis will evaluate whether to terminate Cohort B for futility or potentially adapt Cohort B Part 2 dose levels and randomization ratio based on the predictive probability of achieving a significant difference of enpatoran 100 mg BID vs placebo at Week 24 at the final analysis, given the interim data on BICLA response at Week 24. The methodology and the pre-specified rules are described in the interim IAP.

- A second interim analysis will be conducted at the same time to support potential adaptation of dose group(s) and randomization ratio for Cohort B Part 2 (e.g., assigning newly enrolled participants to other dose levels, adapting the randomization ratio) to improve dose-finding in SLE. These adaptations will not apply to participants randomized in Cohort B Part 2 prior to the adaptation decision. Information on the input data, methodology and the guiding principle underlying the recommendation for adaptation are provided in the interim IAP.

Details of these interim analyses are specified in a separate interim IAP provided in appendix 18.3.

6.4 Primary Analysis for Cohort A

This analysis will be the primary analysis for Cohort A. Related analyses identified in this IAP will be performed after all participants in Cohort A have completed Week 16 visit or discontinued the study early, and the database is partially locked for the analysis. Apart from adverse events and treatment exposure data, only data from Cohort A collected up to Week 16 (or earlier discontinuation) will be part of the analysis.

The analyses to be provided for the primary analysis of Cohort A are specified in the different sections of the IAP and in the table of objectives and estimands from section 5.

6.5 Final Analysis of Cohorts A and B

Related analyses will be performed after all participants (from Cohorts A and B) have completed the safety follow-up visit at Week 26, have entered the long-term extension study as part of a separate Sponsor protocol, or have early discontinued the study, and the database is locked for the analysis. The final analysis of data for Cohort A and Cohort B may be performed at the same time or sequentially at the discretion of the Sponsor depending on the time of each cohort's completion.

The analyses to be provided for the final analysis are specified in the different sections of the IAP and in the table of objectives and estimands from section 5.

7 Changes to the Planned Analyses in the Clinical Study Protocol

Section 8.1: the definition of the FAS has been updated to exclude participants who were not randomized in the cohort they were eligible to. Additionally, participants randomized in Cohort B with no BILAG A and no BILAG B at Day 1 will be excluded from the FAS.

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CCI [redacted]

8 Analysis Sets and Subgroups

8.1 Definition of Analysis Sets

Each analysis set will be described for each cohort separately, unless specified otherwise.

Screening Analysis Set (SCR)

The screening analysis set (SCR) includes all participants who signed the informed consent, regardless of the participant's randomization and study intervention status in the study.

Full Analysis Set (FAS)

The Full Analysis Set (FAS) will include all participants randomized in the cohort to which they were eligible. Participants with SLE included in Cohort A with ≥ 1 BILAG A score and/or ≥ 2 BILAG B scores at Screening and participants with SLE included in Cohort B with no BILAG A score and < 2 BILAG B scores at Screening will be excluded from the FAS. Participants randomized in Cohort B with no BILAG A and no BILAG B at Day 1 (randomization) will also be excluded from the FAS. Participants will be analyzed according to the study intervention assigned at randomization as per the intent-to-treat principle. For participants who were randomized by mistake more than once with different participant identifiers, the first randomization will be used in this analysis set.

Safety Analysis Set (SAF)

The Safety Analysis Set (SAF) will include all participants, who were administered any dose of any study intervention. Participants will be analyzed per the first actual study intervention they received.

PK Analysis Set (PKAS)

The PK Analysis Set (PKAS) is a subset of the SAF and will consist of all participants, who receive at least one dose of study intervention, have no important events affecting PK, and provide at least one measurable post-dose concentration. A measurement below lower limit of quantification (BLQ) is considered a valid measurement. Participants will be analyzed per the actual study intervention they received.

Pharmacodynamic Analysis Set (PDAS)

The PD analysis set (PDAS) will include all participants who received at least one dose of study intervention, have no important events affecting PD, and have at least one baseline higher or equal to the lower limit of quantification (LLOQ) and one measurable PD endpoint post-dose. Participants will be analyzed per the actual study intervention they received. Important events affecting PD include participants with SLE included in Cohort A with ≥ 1 BILAG A score and/or ≥ 2 BILAG B scores at Screening and participants with SLE included in Cohort B with no BILAG A score and < 2 BILAG B scores at Screening.

Analyses per Analysis Set

The following table summarizes the use of the analysis sets in the different analyses.

	Analysis Set			
Analyses	**FAS**	**SAF**	**PKAS**	**PDAS**
Demographics and Other Baseline Characteristics	✓			
Previous and Concomitant Therapies	✓			
Study Intervention: Compliance and Exposure		✓		
Efficacy Analyses	✓			
Safety Analyses		✓		
Pharmacokinetics			✓	
Pharmacodynamics				✓

8.2 Subgroup Definition and Parameterization

Subgroup analyses will be performed for primary efficacy variables (BICLA response at Week 24 in Cohort B [section 14.2.5], CLASI-A total score at Week 16 in Cohort A [section 14.1.6]), selected key secondary variables (SRI-4 response at Week 24 in Cohort B [14.3.6]), and CCI [redacted]

The category "missing" will not be included in any subgroup analysis. In Cohort A, subgroup analysis will be performed if at least 5 participants are observed in all subgroup levels for each study intervention group. The threshold will be set to 10 for subgroup analyses in Cohort B.

CCI [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- CCI [redacted]
- [redacted]
- [redacted]
- Systemic CS use at Baseline: low/medium (daily prednisone-equivalent dose < 10 mg), high (daily prednisone-equivalent dose ≥ 10 mg)

The following subgroups will be defined for Cohort A only:

- Disease diagnosis (CLE only, SLE)

  CLE only: "Does the subject have a diagnosis of SLE" = No and participant has DLE and/or SCLE

  SLE: "Does the subject have a diagnosis of SLE" = Yes
- CLASI-A total score at Baseline: < 10, ≥ 10

The following subgroups will be defined for Cohort B only:

- CCI
  - [redacted]
    - [redacted]
    - [redacted]
    - [redacted]
  - [redacted]
- CCI
- Ethnicity: Japanese, non-Japanese

The following subgroups will be defined for Cohort B with CLASI A ≥ 8 at Screening and confirmed at Day 1:

- CLASI-A total score at Baseline: < 10, ≥ 10

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- [redacted]
- [redacted]
- [redacted]

9 General Specifications for Data Analyses

Unless otherwise specified, data will be summarized for each cohort (Cohort A, Cohort B) separately.

Study intervention groups will be labeled placebo, enpatoran 25 mg BID and enpatoran 50 mg BID, enpatoran 100 mg BID, as applicable for the cohort/part. Study intervention groups may also be referred as "dose levels".

Unless otherwise specified, comparisons will be presented for each active dose of study intervention versus placebo. Results from different study intervention groups will be presented in increasing order of dose level (placebo on the left).

Unless otherwise specified, continuous variables will be summarized using descriptive statistics, i.e., the number of participants with non-missing values (n), mean, standard deviation, median, 25th percentile (Q1) and 75th percentile (Q3), minimum, and maximum.

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise stated the calculation of proportions will be based on the number of participants of the analysis set of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

Unless otherwise specified, descriptive statistics by nominal visit or time point, e.g., for laboratory measurements, will include data from both scheduled and unscheduled visits after applying visit/time windowing (section 9.7). Unscheduled visits will also be included in the derivation of baseline or worst post-baseline values.

CCI [redacted] If confidence intervals are to be calculated, these will be two-sided with a confidence probability of 95%, unless otherwise specified in this IAP.

In order to provide overall estimates of study intervention effects, data will be pooled across sites. The "site" factor will not be considered in statistical models due to the high number of participating sites in contrast to the anticipated small number of participants randomized at each site.

All statistical analyses described in this IAP will be performed using SAS® software version 9.4 or higher apart from the analysis of the primary estimands using the MCP-Mod approach which will be performed using R version 4.1.3 or higher. Phoenix® WinNonlin® version 8.3 or higher (Certara, L.P., Princeton, New Jersey, USA) will also be used to derive PK parameters.

9.1 Data handling for Cohort A Primary Analysis

By the nature of Cohort A primary analysis, Cohort A data after Week 16 may be incomplete and subject to further change. Cohort A data after Week 16 will not be used for summary statistics, statistical analyses, listings or imputations, with the exception of all available adverse events and treatment exposure data that will be included in the analysis.

9.2 Definition of Baseline and Change from Baseline

In general, the last non-missing measurement prior to the first administration of study intervention will serve as the baseline measurement. In case a participant was randomized but did not receive the study intervention, the last non-missing measurement prior to the date of randomization will be used as baseline value.

For all efficacy endpoints of Section 14, only assessment date, but not the hours, will be used in the derivation of baseline value, i.e., an assessment collected the same day but after the first administration of study intervention will be considered for the derivation of baseline value.

For other endpoints, if an assessment which is planned to be performed before randomization or study intervention per protocol is performed on the same day as the randomization or start of study intervention, respectively, but the assessment time is not available, it will be assumed that it was performed prior and will be considered for derivation of baseline.

Absolute and percent changes from Baseline are defined as

absolute change = visit value – baseline value

percent change = 100 * (visit value – baseline value) / baseline value

9.3 Study Day / Study Intervention Day

Day 1 is the day of first dose of study intervention, the day before is Day -1 (no Day 0 is defined). Study day / Study intervention day is defined relative to Day 1.

9.4 Definition of Duration and 'Time Since' Variables

Durations in days will be calculated by the difference of start and stop date + 1 (e.g., AE duration (days) = stop date – start date + 1) if not otherwise specified.

The time since an event (e.g., time since documented diagnosis) will be calculated as reference date minus date of event.

9.5 Conversion Factors

The following conversion factors will be used:

- 1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days
- 1 kg = 2.20462 lbs
- 1 cm = 0.39370 in
- From °F to °C: (°F – 32) / 1.8000

9.6 Date of Last Contact

The date of last contact will be derived for all participants using the latest complete date prior to or at the data cut-off date among the following:

- AE start and end dates
- Date of last study intervention
- Date for any study assessments
- Date of study completion/discontinuation
- Date of death

Only dates associated with actual examinations of the participant reported in the eCRF will be used in the derivation. Dates associated with a technical operation unrelated to participant status such as the date a blood sample was processed will not be used.

9.7 Time Window

Unless otherwise specified, study measurements will be assigned an analysis visit based on their actual assessment date as described in the table below.

Analysis Visit	Target Day	Window Range
Day 1	1	1
Week 2 Day 15	15	> 1 – 21
Week 4 Day 29	29	22 – 42
Week 8 Day 57	57	43 – 70
Week 12 Day 85	85	71 – 98
Week 16 Day 113	113	99 – 126
Week 20 Day 141	141	127 – 154
Week 24 Day 169	169	155 – 176
Safety Follow-up Visit Week 26 Day 183	183	≥ 177

For the Cohort B final analysis, the following table will be used:

Analysis Visit	Target Day	eCRF visit	Window Range
Day 1	1	Any	1
Week 2 Day 15	15	Any	> 1 – 21
Week 4 Day 29	29	Any	22 – 42
Week 8 Day 57	57	Any	43 – 70
Week 12 Day 85	85	Any	71 – 98
Week 16 Day 113	113	Any	99 – 126
Week 20 Day 141	141	Any	127 – 154
Week 24 Day 169	169	Any	155 – 176
		Any apart from Safety Follow-up visit	177 – 182
Safety Follow-up Visit Week 26 Day 183	183	Safety Follow-up visit	177 – 182
		Any	> 182

In case multiple assessments are assigned to the same window, the closest value to the target day will be considered for analysis. If two values are observed with the same distance to the target day (one before and one after), then the earlier value will be used for analysis.

In case several time points are scheduled on a same day, specifications will be provided for the related parameters. For parameters not expected to be collected at each visit, visit windows will be combined. As an example, if a parameter is not measured at Week 2, the Week 4 visit window will extend from > 1 to 42.

9.8 Definition of On-treatment Period

The on-treatment period is defined as the time from the first dose of study intervention to the date of last contact.

9.9 Exposure time

Duration of exposure to study intervention = end date – date of first dose of study intervention +1, where:

- end date is the date of last dose of study intervention.

9.10 Imputation of Missing Data

Disease history:

Incomplete dates for documented diagnosis of CLE or SLE will be imputed as follows:

- If the day is missing, it will be imputed to the 1st day of the month.
- If both day and month are missing and the year is available, the month and day will be imputed as January 1st.
- If the date is completely missing, no imputation will be performed.

Exposure:

In case the start date of study intervention is missing, it is assumed that the first dose of study intervention is given at the randomization date. The randomization date will replace incomplete dates of the first dose of study intervention.

Adverse events:

Incomplete AE-related dates will be imputed as follows:

- In case the onset date is missing completely or missing partially but the onset month and year, or the onset year are equal to the start of study intervention then the onset date will be imputed by the minimum of start of study intervention and AE resolution date (if not missing).
- In all other cases, the missing onset day or missing onset month will be imputed by 1.
- Incomplete stop dates will be imputed by the last day of the month (if day is missing only), if not resulting in a date later than the date of participant's death. In the latter case, the date of death will be used to impute the incomplete stop date.
- In all other cases, the incomplete stop date will not be imputed.

Previous and concomitant medication:

Incomplete previous/concomitant medication start and stop dates will be imputed as presented in Table 1~~Table 1~~.

For the derivation of previous and concomitant medications, the following rules will be applied:

Previous Medication:

- Start date ≤ Start of study intervention OR
- Start date = Missing

Concomitant Medication:

- End date ≥ Start of study intervention AND (Start date ≤ End of study intervention OR Start date=Missing) OR
- End date = Missing AND (Start date ≤ End of study intervention OR Start date = Missing)

Table 1 Imputation rules for missing/incomplete start/end dates of medication

	Start Date	End Date
Day missing only	Day = 1	Day = Last day of month
Month missing	Day = 1 Month = Jan	Day = 31 Month = Dec
Year missing	Date = Missing No imputation	
All	if imputed date > date of death: imputation by date of death	

Concentration for pharmacodynamics/biomarkers:

For calculation of descriptive statistics, values below the lower limit of quantification will be set to half of the lower limit value (LLOQ). BLQ will be reported in participant data listings.

Missing data imputation related to the clinical efficacy questionnaires and efficacy estimands will be described in the corresponding sections.

In all participant data listings, imputed values will be presented, and imputed information will be flagged.

Missing statistics, e.g., when they cannot be calculated, should be presented as “ne” (not estimable). For example, if n=1, the measure of variability (SD) cannot be computed and should be presented as “ne”.

9.11 Scoring and Handling of Missing Item-level Data for Clinician-Reported Outcomes

9.11.1 CLASI

Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) is a validated measurement instrument for lupus erythematosus developed for use in clinical studies that consists of 2 separate scores evaluating disease activity (CLASI-A) and damage (CLASI-D). The activity scale includes measurements of erythema, scale /hypertrophy, active alopecia, recent hair loss and mucous membrane disease, whereas the damage scale measure dyspigmentation, atrophy, and scarring.

Scores range from 0 to 70 points for CLASI-A total score. Mild, moderate, and severe disease corresponds to CLASI activity score ranges of 0 to 9, 10 to 20, and 21 to 70, respectively.

The CLASI-A total score as collected in eCRF will be used in the analysis. Sub-scores will be computed using individual items. Erythema sub-score will be computed as the sum of scores obtained after rating of erythema for each of the 13 body areas. Scale/hypertrophy sub-score will be computed as the sum of scores obtained after rating of scale/hypertrophy for each of the 13 body areas. Erythema sub-score ranges from 0 to 39. Scale/hypertrophy sub-score ranges from 0 to 26.

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9.11.3 BILAG 2004

The BILAG 2004 Disease Activity Index evaluates SLE activity in a number of 9 organs or systems.

A separate alphabetic score is assigned to the 9 organs or systems, corresponding in general to the following definitions:

- BILAG A: Severe disease activity requiring any of the following treatments (e.g., systemic high dose oral CS, intravenous pulse CS, systemic immunosuppressants, or therapeutic high dose anticoagulation in the presence of high dose CS or ≥ 20 mg prednisone).
- BILAG B: Moderate disease activity requiring treatment with systemic low-dose oral glucocorticoids, intramuscular or intra-articular or soft tissue CS injection, topical CS or immunosuppressants, or symptomatic therapy such as antimalarials or NSAIDs
- BILAG C: Mild disease
- BILAG D: System previously affected but now inactive
- BILAG E: System never involved

The BILAG 2004 is evaluated by scoring each of a list of signs and symptom as: improving (1); same (2); worse (3); new (4); not present (0); not done (nd). For some items, appropriate responses may be: Y/N or numerical values where indicated, or Y/N confirm this is due to SLE activity.

The grade scoring for each organ domain is provided in appendix 18.1.1.

Handling of missing items:

Single imputation will be done at the item level unless the questionnaire is ticked as Not done. For all organ domains, missing items (including 'Not done') will be imputed using the value carried forward from the preceding analysis visit (only value observed after Baseline can be used for imputation and no imputation can be done from a value previously imputed itself).

For BILAG 2004 associated laboratory tests CCI [redacted] results may only be available as per Investigator's opinion. If not available, they are not considered as missing, but as not applicable and will not be imputed. This applies to items 95, 96 and 97 from the hematological domain (respectively thrombotic thrombocytopenic purpura [TTP], evidence of active hemolysis and Coombs' test positive).

If after imputation of missing items, the score cannot be assigned to the organ or system at the visit, then it will be considered as missing.

9.11.4 Physician's Global Assessment of SLE Disease Activity

Physician's global assessment (PGA) of SLE disease activity is collected in the eCRF on a 0-100 mm scale. It is used on 0-3-point scale in the derivation of systemic lupus erythematosus responder index (SRI), LLDAS and remission attainment and CCI flare index. The PGA should then be transformed as: PGA score = PGA (mm) * 3/100.

9.11.5 28-Joint Count Questionnaire

The 28-joint count questionnaire assesses 14 joints on each side (28 joints overall) for both tenderness and swelling. The outcome for the assessment of each joint can be "absent", "present", "replaced" or "unable to evaluate".

Tender 28-joint count will be derived as the count of joints which are tender.

Swollen 28-joint count will be derived as the count of joints which are swollen.

The number of tender and swollen joints will be calculated as the count of joints which are both tender and swollen.

If a joint has been replaced during the on-treatment period, the last observed value (present or absent) will be used for all assessments after the replacement. If a joint was already replaced at Baseline, the participant will not be included in the analysis. If a joint assessment is unable to evaluate or missing, the last observed value will be used.

9.12 Scoring of Patient-Reported Outcomes

9.12.1 Skindex-29+3

The Skindex-29+3 is a self-reported measure of skin-specific symptoms and functioning for CLE populations, and includes items from the Skindex-29, and 3 lupus-specific items.

It is composed of 33 items rated on a 5-point Likert-type scale ranging from 1 = "never" to 5 = "all the time" (Mapi Research Trust 2020). Note that item #18 is not included in the calculation of the scores.

Table 2: Skindex-29+3 domains/subscale

Domain/Subscale	Number of items	Number of non-missing items necessary to calculate the score	Cluster of items
Emotion	10	8	3; 6; 9; 12-13; 15; 21; 23; 26; 28
Symptoms	7	6	1; 7; 10; 16; 19; 24; 27
Functioning	12	9	2; 4; 5; 8; 11; 14; 17; 20; 22; 25; 29-30
Lupus-specific	3	3	31; 32; 33

Photosensitivity	2	2	31; 33

Each item score must be transformed on a linear 0-100 scale:

- 1 (never) = 0
- 2 (rarely) = 25
- 3 (sometimes) = 50
- 4 (often) = 75
- 5 (all the time) = 100

The domain scores (0-100) are the average of the non-missing item scores as shown in Table 2~~Table 2~~. For all scores, higher scores indicate lower functioning/worse symptoms.

An item with multiple answers is considered missing. The minimum number of non-missing items necessary to compute each domain score is reported in Table 2~~Table 2~~.

9.12.2 FACIT-Fatigue

The FACIT-Fatigue is a 13-item questionnaire assessing self-reported fatigue and its impact upon daily activities and function (Yellen 1997). Each item is rated using a 5-point Likert-type scale (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; 4 = very much). The item scores will be transformed in the following way

$$R_i := \begin{cases} 4 - I_i, & for\ i = 1,2,3,4,5,6,9,10,11,12,13 \\ I_i, & for\ i = 7,8 \end{cases}, \quad (1)$$

where I_i is the item score for item i. This way, 0 is the worst and 4 is the best outcome for "positively" and "negatively worded" items. The sum of transformed item responses $\sum_{i=1}^{13} R_i$ must be multiplied by 13 and divided by the number of non-missing items to obtain the FACIT-Fatigue score. Its range is 0-52, with 0 being the worst possible score and 52 the best possible score. The FACIT-Fatigue score can be calculated if more than 50 % of the items are answered, i.e., 7 out of 13 items (https://www.facit.org/scoring), otherwise it will be considered as missing.

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10 Study Participants

The subsections in this section include specifications for reporting participant disposition and study intervention/study discontinuations. Additionally, procedures for reporting protocol deviations are provided. Unless otherwise specified, all the related outputs will be provided for the primary analysis of Cohort A and the final analysis.

10.1 Disposition of Participants and Discontinuations

The number and percentage of participants in each of the below disposition categories will be presented for each cohort separately by cohort, study intervention groups and overall. Percentages will be presented with respect to the number of randomized participants.

- Total number of participants screened (i.e., participants who gave informed consent)
- Number of participants who discontinued the study prior to randomization overall and grouped by the main reason (Subject did not meet all eligibility criteria, Withdrawal by subject, Progressive disease, Adverse event, Lost to follow-up, Death, Other)
- Number and percentage of randomized participants.
    - Number and percentage of participants randomized in error for each cohort

The end of study intervention status will be summarized by:

- Number and percentage of randomized participants who did not receive any dose of study intervention
- Number and percentage of randomized participants with ongoing study intervention (primary analysis of Cohort A only)
- Number and percentage of randomized participants who completed study intervention
- Number and percentage of randomized participants who discontinued the study intervention (overall and by primary reason)
- Number and percentage of randomized participants who discontinued the study intervention due to COVID-19

The end of study status will be summarized by:

- Number and percentage of randomized participants still on-study (primary analysis of Cohort A only)
- Number and percentage of randomized participants who completed or prematurely discontinued the study after randomization, grouped by main reason
- Number and percentage of randomized participants who discontinued the study due to COVID-19

Additionally, the number of participants screened, and included in each analysis set will be provided overall, by region (North America, Western Europe, Eastern Europe, South America, Asia, Rest of the world), by country within region and by site.

The results of the randomization algorithm (according to IWRS) will be summarized at primary analysis in Cohort A and at final analysis in Cohort B as follows:

- Number of randomized participants overall, by region (North America, Western Europe, Eastern Europe, South America, Asia, Rest of the world), by country within region
- Number of randomized participants by randomization strata (source: IWRS)
- Number of randomized participants by randomization strata (source: eCRF or central laboratory)
- Cross tabulation: participants randomized (placebo, enpatoran CCI 100 mg BID) vs. treated (placebo, enpatoran 50 mg BID, 50 mg BID, 100 mg BID, not treated)

Disposition of PRO Questionnaires

The disposition of PRO questionnaires will be described (by cohort and study group intervention) for Skindex-29+3 subscales and FACIT-Fatigue separately at Baseline and Week 24 in terms of completion and compliance rates as described below:

- Number of randomized participants for whom the visit is expected
- Number and percentage of randomized participants who returned the questionnaire at the visit as expected CCI

$$\%\ \text{Compliance} = 100 \times \frac{\text{number of participants who returned the PRO questionnaire}}{\text{number of participants for whom a PRO questionnaire is expected}}$$

A questionnaire is considered returned if at least one item from the questionnaire is answered.

- Number and percentage of randomized participants with at least one evaluable questionnaire subscale at the visit (completion rate using all expected PRO questionnaires in the denominator)

$$\%\ \text{Completion} = 100 \times \frac{\text{number of participants with at least one evaluable PRO subscale}}{\text{number of participants for whom a PRO questionnaire is expected}}$$

A questionnaire is considered evaluable if PRO scores can be derived according to scoring manual for at least one subscale.

Reasons for non-completion and non-compliance of Skindex-29+3 and FACIT-Fatigue questionnaires will also be described (by cohort and study group intervention) at Baseline and Week 24 as follows:

- Number and percentage of randomized participants with non-expected questionnaire at the visit by reason – reasons for non-compliance:
  - Death
  - Lost to follow-up
  - Withdrawal by subject
  - Other reason for study termination
- Number and percentage of randomized participants with missing questionnaire at the visit by reason while expected – reasons for non-completion:
  - Subject felt too ill
  - Clinician or nurse felt the subject was too ill
  - Subject felt it was inconvenient
  - Subject felt it takes too much time
  - Subject felt it was not relevant
  - Subject felt it was a violation of privacy
  - Subject did not understand the actual language
  - Administrative failure to distribute the questionnaire to the subject
  - Subject unable to come to site
  - Site was closed
  - Investigator decision
  - Subject did not come for unknown reasons
  - Other
  - Non-completion due to COVID-19 (Yes, No)

10.2 Protocol Deviations / Exclusion from Analysis Sets

10.2.1 Important Protocol Deviations

Important protocol deviations (IPDs) are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being.

All protocol deviations (important and non-important) will be documented in SDTM datasets whether identified through site monitoring, medical review or programming.

A frequency table of important protocol deviations will be provided based on the FAS by cohort and study intervention group. This table will present the number of participants with at least one important protocol deviation overall, per category and per deviation description.

10.2.2 Reasons Leading to the Exclusion from an Analysis Set

A listing of participants excluded from the SAF, FAS, PK, and/or PD analysis sets including the associated reason(s) will be provided.

11 Demographics and Other Baseline Characteristics

If not stated otherwise, the following analyses will be performed based on the FAS by cohort, study intervention group and overall within each cohort. They will be conducted for the final analyses of Cohort A and Cohort B. Items from Section 11.1 and 11.3 identified with an asterisk (*) will also be analyzed for the primary analysis of Cohort A.

11.1 Demographics

Demographic characteristics and physical measurements will be summarized descriptively using the following information from the Screening/Baseline visit eCRF pages.

The following demographic characteristics will be included:

- Sex (*): male, female
- Race (*):
    - American Indian or Alaska Native
    - Asian
        - Chinese, Japanese, Korean, Other Asian
    - Black or African American
    - Native Hawaiian or Other Pacific Islander
    - White
    - More than one race

        - All combinations
    - Other
    - Not permitted per local regulation
- Ethnicity (*): Hispanic or Latino, Not Hispanic or Latino, Not permitted per local regulation
- Age (years) as collected in eCRF (*)
- Age categories (*):
    - <= 45 years
    - > 45 - <= 65 years,
    - > 65 years
- Pooled Region 1 (used by IWRS) (*):
    - North America and Western Europe
    - Asia
    - Central/South America and Rest of the World
- Pooled Region 2 (*):
    - North America and Europe
    - Asia
    - Central/South America and Rest of the World
- EEA (European Economic Area) (*): Yes, No
- Weight (kg)
- Body surface area (BSA) (m^2)

  $$BSA\ [m^2] = \sqrt{\frac{height\ [cm] \cdot weight\ [kg]}{3600}}$$
- BMI (kg/m^2)

  $$BMI\ [kg/m^2] = \frac{weight\ [kg]}{height[cm]^2} \cdot 10000$$

11.2 Medical History

The medical history will be summarized from the "Medical History" eCRF page, using the most recent MedDRA version at time of database lock, preferred term as event category and system organ class (SOC) body term as body system category. Each participant will be counted only once within each PT or SOC.

Medical history will be displayed by a frequency table ordered by primary SOC and PT in alphabetical order.

11.3 Other Baseline Characteristics

Information on disease characteristics collected at Baseline will be summarized. Summary statistics will be presented for:

For Cohort A and Cohort B separately:

- Participants with SLE (derived as response to question "Does the subject have a diagnosis of Systemic Lupus Erythematosus (SLE)?"=Yes)
- Participants who meet SLICC criteria for SLE (≥ 4 SLICC criteria met with at least 1 clinical criterion and 1 immunological criterion (see Appendix 18.1.4)
- Each of the SLICC criteria: yes (including details), no
- Participants who meet ACR 1997 criteria for SLE (≥ 4 ACR criteria met) (see Appendix 18.1.5)
- Each of the ACR 1997 criteria: yes (including details), no
- Participants who meet 2019 EULAR/ACR criteria for SLE (see Appendix 18.1.3 for derivation)
- Each of the EULAR/ACR criteria: yes (including details), no
- Participants with both SLE and CLE (*):

  - Subacute Cutaneous Lupus (SCLE)
    - Active rash: Yes, No
  - Discoid Lupus (DLE)
    - Active rash: Yes, No
  - CCI [redacted]
  - [redacted]
  - [redacted]

- Time since first documented diagnosis (years) for CLE and SLE separately (*)

  See Section 9.10 for handling of incomplete dates.

  If a participant has several CLE subtypes (SCLE and DLE), the oldest date of CLE diagnosis will be used whether the diagnosis is currently active or not.

Disease activity at Baseline (*):

- CLASI-A total score at Baseline, described as a continuous variable, as well as categorized as 'mild' (score ranges from 0 to 9), 'moderate' (score ranges from 10 to 20) and 'severe' (score ranges from 21 to 70).

  CLASI-A will be summarized separately in the whole cohort, in CLE participants of the cohort and in SLE participants of the cohort.

  Participants' CLASI-A total score will also be depicted using a histogram grouped by study intervention group.

- CLASI-A erythema score (see Section 9.11.1 for derivation), described as a continuous variable.
- CLASI-A scale/hypertrophy score (see Section 9.11.1 for derivation), described as a continuous variable, and categorized as 0 vs > 0.

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- BILAG severity score at Baseline (Cohort B only), described as follows:
  - Severe = At least 1 BILAG A

- Moderate = At least 2 BILAG B and no BILAG A
- Mild = No BILAG A and no more than 1 BILAG B

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Renal Function at Baseline:

- Individualized eGFR (mL/min)

  Derived from standardized eGFR (mL/min/1.73m²) calculated from MDRD formula and converted to mL/min using participant's BSA.

- Individualized eGFR categorized as:
  - Normal (≥ 90 mL/min)
  - Mild impairment (60-89 mL/min)
  - Moderate impairment (30-59 mL/min)
  - Severe impairment (15-29 mL/min)
  - Kidney failure (< 15 mL/min)

12 Previous or Concomitant Therapies/Procedures

The following analyses will be performed based on the FAS by cohort and study intervention group. All these analyses will be provided at final analyses of Cohort A and Cohort B. Analysis of background therapy received at Baseline will also be provided at primary analysis of Cohort A.

Concomitant medications are medications, other than study intervention, which are taken by participants any time during the on-treatment period (see section 9.8).

Previous medications are medications other than study intervention which started before the first administration of study intervention.

A medication may be classified as both concomitant and previous. The respective flags will be derived based on start and end date (see section 9.10 for derivation).

Previous and concomitant medications will be summarized by the number and percentage of participants. Preferred term within ATC Classification code level 2 will be tabulated as given from the WHO-DD dictionary most current version.

If any previous or concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes.

The summary tables will be sorted by decreasing frequency of drug class and decreasing frequency of preferred term in a given drug class. In case of equal frequency regarding ATC classification level 2 or preferred term, alphabetical order will be used.

In case any specific medication does not have an ATC classification level 2 coded term, it will be summarized under "Unavailable ATC classification" category. Each participant will only be counted once, even if he/she received the same medication at different times.

Background therapy at Baseline:

- Systemic CS use at Baseline (yes, no)
- Daily prednisone-equivalent CS dose at Baseline (mg) as a continuous variable (see appendix 18.2 for derivation)
- Daily prednisone-equivalent CS dose at Baseline (mg) categorized as below:
  - $< 10, \geq 10$
  - $\leq 5, > 5 - \leq 7.5, > 7.5 - < 10, \geq 10 - < 15, \geq 15 - < 20, \geq 20$
- Topical CS use at Baseline (yes, no)
- Number and percentage of participants taking immunosuppressants, excluding antimalarials, at Baseline (yes, no) and details by medication (azathioprine, retinoids, leflunomide, methotrexate, mycophenolate [includes mycophenolate mofetil, mycophenolate sodium, mycophenolic acid], tacrolimus, other)

  Use of immunosuppressant will be derived at Day 1 using concomitant medications data with class = "Immunosuppressant", Anatomical Therapeutic Chemical (ATC) code level 3 = L04A, excluding medications also coded under P01B ATC code level 3 category (i.e., Chloroquine, Chloroquine sulfate, Hydroxychloroquine, Hydroxychloroquine sulfate).

- Number and percentage of participants taking antimalarials at Baseline (yes, no)

  Use of antimalarials will be derived at Day 1 using concomitant medications data with class = "Antimalarials", ATC code level 3 = P01B.

The following information will be summarized during the on-treatment period:

- Systemic CS use (yes, no)
- Topical CS use (yes, no)
- Number and percentage of participants taking immunosuppressants, excluding antimalarials, (yes, no) and details by medication (azathioprine, retinoids, leflunomide, methotrexate, mycophenolate [includes mycophenolate mofetil, mycophenolate sodium, mycophenolic acid], tacrolimus, other)
- Number and percentage of participants taking antimalarials (yes, no)

The following listings will be provided:

- Previous and concomitant medications
- Concomitant procedures
- Chest imaging

13 Study Intervention: Compliance and Exposure

The following analyses will be performed based on the safety analysis set by cohort and study intervention group. They will be conducted for the primary analysis of Cohort A and the final analysis. All dosing calculations and summaries will be based on "Study Treatment Administration Details" eCRF page.

The duration of exposure to study drug in weeks will be calculated according to the following formula:

Treatment duration (weeks) = (date of last administration received – date of first administration received + 1)/7

Treatment duration will be summarized as a continuous variable and according to the following categories (≤ 2 weeks, > 2 - ≤ 10 weeks, > 10 - ≤ 14 weeks, > 14 - ≤ 22 weeks, > 22 weeks).

Cumulative dose (mg) is defined as the sum of all actual doses of study intervention taken during the study and will be summarized for all active study intervention groups as a continuous variable. A participant may have different dosing intervals. Total cumulative dose will then be computed as the sum of the cumulative doses received during each constant-dosing interval. Cumulative dose received during the dosing interval will be computed as:

- (date of last dose – date of first dose + 1) * number of tablets taken * r * 25, where r is the fraction of tablets containing enpatoran 25 mg for the kits dispensed during this interval: r=0 for placebo, r=1/4 for enpatoran 25 mg BID, r=1/2 for enpatoran 50 mg BID, r=1 for enpatoran 100 mg BID

Compliance (%) with study intervention will also be summarized. It will be computed as follows:

$$Compliance = 100 \times (\frac{N_1}{8 \cdot N_2})$$

where

- N1 = total number of tablets taken during the study,
- N2 = date of last dose – date of first dose + 1.

It will also be summarized using the following categorization: < 80%, 80% - 125%, > 125%.

The following by-participant data listings will be provided for final analyses:

- Listing of start/end dates of each constant-dosing interval together with the number of tablets ingested during that interval and reason for change in dose.
- Listing of start date and time of administrations on site, dose timepoint, date and time of last and first meal before and after administration respectively.
- Listing with exposure time, cumulative dose, and compliance.

14 Efficacy Analyses

The following analyses will be performed based on the FAS by study intervention group. Unless otherwise specified, the visit window algorithm described in Section 9.7 will be applied to all efficacy assessments. CCI

14.1 Primary Estimand - Cohort A: Percent Change in CLASI-A at Week 16

The primary, sensitivity, supportive and subgroup analyses of this estimand will be conducted on the FAS, in participants from Cohort A. For the primary analysis of Cohort A, only analyses described in Sections 14.1.1, 14.1.2, 14.1.3, and 14.1.6 will be performed.

14.1.1 Primary Objective – Cohort A: Derivation and Analysis of the Primary Estimand

The primary efficacy variable in Cohort A is the percent change from baseline in CLASI-A at Week 16.

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Descriptive Analysis:

Observed CLASI-A (absolute value, change and percent change from Baseline) will be summarized using descriptive statistics at each analysis visit from Baseline to Week 26. A boxplot of percent changes from Baseline in CLASI-A by analysis visit will also be produced. A line graph of the mean score with 95% CI by treatment arm will supplement this visualization for CLASI-A total score.

Inferential Analysis:

A 2-stage generalized MCP-Mod approach will be used (Pinheiro 2014) to allow for covariate adjustment (stratification factors and baseline CLASI-A total score) and imputation of missing data. In the first stage, an analysis of covariance (ANCOVA) model will be fitted to the data after multiple imputation to obtain $\hat{\mu}$ the vector of covariate-adjusted estimates for each study intervention group, as well as $\hat{S}$ the associated covariance matrix. In a second stage, MCP-Mod will be performed on these summary estimates in ways similar to the original 2-step MCP-Mod approach:

- Step 1: A multiple comparison procedure which aims at establishing a proof of concept, i.e., detecting a statistically significant dose-response signal. This step will be performed using a multiple contrast test adjusting for the multiple candidate dose-response models.
- Step 2: If dose-response has been established (MCP step showed a statistically significant result at 2.5% alpha level), dose-response is estimated based on the best selected dose-response model.

The generalized MCP-Mod approach will be programmed using the DoseFinding package from R.

Stage 1: Handling of missing data and covariate adjustment

Missing data will be handled using multiple imputation assuming missing at random (MAR). As a preliminary step, intermittent missing data will be imputed using the MCMC (Markov Chain Monte Carlo) method. Then, missing values will be imputed under the assumption of monotone missing data patterns (O'Kelly, M. and Ratitch, B. 2014, Chapter 6). The following variables will be included in the imputation model: region, disease diagnosis, study intervention groups, baseline CLASI-A total score and all scheduled post-baseline CLASI-A total scores until Week 16. A total of 1000 imputed datasets will be produced.

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Then, for each imputed dataset, the percent change from Baseline in CLASI-A total score at Week 16 will be modelled using an ANCOVA with study intervention group, stratification factors, and baseline CLASI-A total score as a continuous variable. The vector of covariate-adjusted means $\hat{\mu}_i$ per study intervention group and their corresponding covariance matrix $\hat{S}_i$ will be estimated from each fitted model.

The 1000 sets of estimates obtained this way will then be combined according to Rubin's rules into a point estimate ($\hat{\mu}$, $\hat{S}$), the vector of covariate-adjusted means by study intervention group and their corresponding covariance matrix.

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Stage 2: MCP step

Six candidate models M(m), m =1 to 6, and their initial parameter estimates were defined as described in Table 3CCI [redacted]

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		/[redacted])	/[redacted])	
		/[redacted])	/[redacted])	

[redacted]

For each candidate model, the optimal contrast will be derived and the null hypothesis H0(m): c(m)' μ = 0 will be tested against the alternative hypothesis H1(m): c(m)' $\mu < 0$, where c(m) is the optimal contrast for the candidate model, using the estimates $\hat{\mu}$ and $\hat{S}$ obtained from the ANCOVA in the previous stage. A multiple contrast test based on the multivariate T-statistic will be performed to get the T-statistic and the corresponding adjusted p-value for each candidate model. This step will be performed using the R function MCTtest.

The global null hypothesis for the Cohort A primary objective of no dose-response will be rejected if at least one of the 6 contrast tests is statistically significant while controlling for the family-wise error rate at 2.5%. In other words, a dose-response for the Cohort A on the percent change from baseline in CLASI-A at Week 16 will be established if at least one adjusted one-sided p-value is < 0.025.

[redacted]

CCI [redacted]

[redacted]

Adjusted means of the percent change from Baseline in CLASI-A total score at Week 16 together with its 95% CI from the selected model will be provided at each dose level. The treatment effect will be estimated for each active dose providing the difference in adjusted means compared to placebo and its 95% CI.

The predicted shape from the selected model together with its 95% confidence band, and the adjusted means (95 % CI) of the percent change from Baseline in CLASI-A total score obtained from ANCOVA model after imputation will also be graphed.

CCI [redacted]

- [redacted]
- [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted] [redacted]

[redacted]

[redacted]

CCI [redacted] [redacted]

[redacted]

- [redacted]
- [redacted]
    - [redacted]
    - [redacted]
- [redacted]

[redacted]

[redacted]

CCI [redacted] [redacted]

[redacted]

An MMRM model will be run to assess treatment effect on percent change from Baseline in CLASI-A score at Week 16 by subgroup level. CCI [redacted]

LS means for percent change from Baseline in CLASI-A at Week 16 and 2-sided 95% CIs will be presented by subgroup level and study intervention group. The difference in the LS means at Week 16 between each study intervention group and placebo, together with accompanying two-sided (non-adjusted) 95% CI, and (non-adjusted) p-value will be provided. Difference in LS means between each study intervention group and placebo and associated 2-sided 95% CI will also be plotted for each subgroup level. The p-value for the test of a significant interaction at Week 16 between the subgroup factor and each study intervention group (Fisher test) will be provided.

14.2 Primary Estimand - Cohort B: BICLA Response at Week 24

The primary, sensitivity, supportive and subgroup analyses of this estimand will be conducted on the FAS, in participants from Cohort B at the time of the final analysis of Cohorts A and B.

14.2.1 Primary Objective – Cohort B: Derivation and Analysis of the Primary Estimand

The primary efficacy endpoint for Cohort B is the response in BILAG-based Composite Lupus Assessment (BICLA) at Week 24, where a participant is BICLA responder if the following criteria are met:

1. BILAG 2004 improvement (all A scores at Baseline improved to B/C/D, and all B scores improved to C or D at Week 24)* AND
2. No worsening in disease activity (no new BILAG 2004 A scores and ≤ 1 new B score at Week 24) compared to Baseline AND
3. No worsening of total CCI [redacted] score at Week 24 from Baseline AND
4. No worsening of ≥ 0.3 points in PGA of SLE disease activity score compared to Baseline (PGA score expressed on a 0 – 3 scale)

* Participants in Cohort B may be included in the FAS with only 1 BILAG B score for a domain. For those, BILAG 2004 improvement will only be assessed on this single domain.

CCI [redacted]

- [redacted]
- [redacted]
- [redacted]

CCI [redacted]

[redacted]

Descriptive Analysis:

The number and percentage of participants with observed BICLA response will be presented during the on-treatment period. The number and percentage of participants meeting each BICLA component criterion will be provided during the on-treatment period. Intercurrent events will also be summarized at each time point.

Inferential Analysis:

The global null hypothesis (H0) for the Cohort B primary objective is the hypothesis that there is no difference in mean BICLA response at Week 24 between study intervention groups. H0 will be tested against the alternative hypothesis H1 of at least one of the active dose levels is superior to placebo at 0.025 alpha level.

Cohort B has a dose-finding adaptive design comprised of 2 parts. First part data and second part data will be analyzed separately to obtain 2 test statistics. Part 1 statistic Z_1 and part 2 statistic Z_2 will then be combined to form a final statistic that will be used to test the global null hypothesis using a weighted inverse normal method (Lehmacher 1999) as follows:

$$Z = \omega_1 Z_1 + \omega_2 Z_2, \text{where } \omega_1 = \frac{\sqrt{60}}{\sqrt{340}} \text{ and } \omega_2 = \frac{\sqrt{280}}{\sqrt{340}}$$

Statistical hypothesis of no difference between study intervention groups will be rejected if $Z \geq z(0.975)$, where $z(0.975)$ is the 97.5%-quantile from the standard normal distribution.

Analysis of Part 1 data – Difference Enpatoran 100 mg BID vs Placebo:

A logistic regression of BICLA response at Week 24 on study intervention group, CCI [redacted] at Screening (source: IWRS) as categorical variables and CCI [redacted] score at Baseline as a continuous variable will be conducted.

Odds ratio together with its 95% CI and the corresponding Part 1 one-sided p-value p_1 will be provided. Z1 will then be computed as $\Phi^{-1}(1 - p_1)$ where Φ is the cumulative standard normal distribution.

The predicted probabilities (with 95% CI) and the difference in predicted probabilities (with 95% CI) between enpatoran 100 mg BID and placebo will be also provided.

Analysis of Part 2 data – Stage 1: covariate adjustment

A generalized MCP-Mod approach similar to that described in section 14.1.1 (primary analysis of CLASI-A in Cohort A) will be used to analyze the BICLA response at Week 24 in Part 2 participants. The analysis will be adjusted for the stratification factors.

In the first stage, a logistic model will be fitted to data to obtain $\hat{\mu}$ the vector of covariate-adjusted mean estimates on the logit scale, as well as $\hat{S}$ the associated covariance matrix.

Analysis of Part 2 data – Stage 2: MCP Step

The optimal contrasts corresponding to the candidate models will be computed as described in section 14.1.1 to get Part 2 p-value p_2 which is defined as the smallest observed p-value among all candidate models.

Z_2 will then be computed as $\Phi^{-1}(1 - p_2)$ where Φ is the cumulative standard normal distribution.

Analysis of Part 2 data – Stage 2: Mod step

Model selection will be performed as described in section 14.1.1.

Covariate-adjusted estimates of the response probability together with their 95% CI will be provided at each dose level. The treatment effect in Part 2 participants will be estimated providing the difference in

predicted probabilities between each active dose and placebo (and their 95% CI). The adjusted estimates of the response probability and their 95% CI will also be graphed.

CCI [redacted]

[redacted]

14.2.3 Sensitivity Analysis 2 of the Primary Estimand regarding the Imputation of Missing data

In the primary analysis described in Section 14.2.1, participants with no available BICLA assessment (after imputation at the item level for CCI [redacted], PGA and BILAG questionnaires) at Week 24 are considered as non-responders. In this sensitivity analysis, ignoring imputation at item level is done for CCI [redacted], PGA and BILAG questionnaires (see 9.11.2 and 9.11.3 respectively), multiple imputation will be performed on BICLA response.

Multiple imputation will be performed under the missingness assumption of MAR. This assumption seems to be realistic given that participants who prematurely discontinued the treatment are considered as non-responder.

To be consistent with the analysis of Part 1 and Part 2 data separately, multiple imputation will also be conducted on the two parts separately.

Each missing component of BICLA response from Week 16 until Week 24 will be imputed. After all components are imputed, BICLA response at Week 24 will be derived in each imputed dataset. A total of 1000 imputed datasets will be produced. The following seed will be used for all imputation models: 1309201521.

Due to the small sample size in Part 1, 4 separate models will be run to impute each BICLA component as described below.

Imputation model for BILAG 2004 improvement (Yes/No) component will include the following variable:

- study intervention group, CCI [redacted] at Screening, baseline hybrid SELENA-SLEDAI score (continuous), BILAG 2004 improvement (Yes/No) at Week 16, Week 20, Week 24

Imputation model for "No worsening in disease activity from Baseline defined as no new BILAG 2004 A scores and ≤ 1 new B score" (Yes/No) component will include the following variable:

- study intervention group, CCI [redacted] at Screening, baseline CCI [redacted] score (continuous), No worsening in disease activity from Baseline (Yes/No) at Week 16, Week 20, Week 24

Imputation model for CCI [redacted] total score related component will include the following variable:

- study intervention group, CCI at Screening, CCI score (continuous) at Baseline, Week 16, Week 20, Week 24

Imputation model for PGA related component will include the following variable:

- study intervention group, CCI at Screening, CCI score (continuous) at Baseline, PGA at Baseline, Week 16, Week 20, Week 24

First, for each of these imputation models, intermittent missing data will be imputed using MCMC (see Section 14.1.1). Subsequently, remaining missing values will be imputed under the assumption of monotone missing data patterns. For continuous variables, the monotone regression method will be used. For binary endpoints related to BILAG questionnaire, previously imputed missing data further to MCMC method will be rounded to the closest integer 0 or 1. Then, the monotone logistic regression will be used to impute remaining missing values.

BICLA response for Part 2 participants will be imputed from a single imputation model including the following variables:

- study intervention group, region, CCI at Screening
- CCI score (continuous) at Baseline, Week 16, Week 20, Week 24
- PGA at Baseline, Week 16, Week 20, Week 24
- BILAG 2004 improvement (Yes/No) at Week 16, Week 20, Week 24
- no worsening in disease activity from Baseline (Yes/No) at Week 16, Week 20, Week 24

As explained above, intermittent missing data will be first imputed using MCMC SAS statement to get a monotone pattern. Then, remaining missing data will be imputed using monotone regression or logistic method depending on the type of variables.

BICLA response will be derived in these 1000 imputed datasets.

For Part 1, the logistic model described in Section 14.2.1 will be run on each imputed dataset. The set of 1000 odds ratios and p-values obtained will be combined according to Rubin's rules and used to get Z1.

For Part 2, the logistic model described in Section 14.2.1 will be run on each imputed dataset. The vector of covariate-adjusted means $\hat{\mu}_i$ and the corresponding covariance matrix $\hat{S}_i$ will be estimated from each fitted logistic model. The set of 1000 estimates obtained this way will then be combined according to Rubin's rules into a point estimate ($\hat{\mu}$, $\hat{S}$), the vector of covariate-adjusted mean estimates on the logit scale and the associated covariance matrix. The rest of the analysis will follow the primary analysis.

14.2.4 Supplementary Analyses of the Primary Estimand

Supplementary analyses described in this section will be performed on all participants from Cohort B (parts 1 and 2 combined). Intercurrent events will be handled similarly to the primary estimand.

Summary statistics for the BICLA response will be summarized during the on-treatment period. The conditional treatment effect on BICLA response at Week 24 will be estimated using a logistic regression model with study intervention group and stratification factors.

Odds ratios and associated two-sided 95% Wald confidence intervals will be provided for each active group versus placebo and will be converted into differences to placebo and their 95% confidence intervals.

An additional supplementary analysis may be performed if 34 Cohort B participants or more (~10 % of the planned sample size in Cohort B) are included in the FAS with no BILAG A score and less than 2 BILAG B scores at Baseline. If this threshold is reached, then the primary analysis described in Section 14.2.1 will be conducted on the subset of the FAS who had at least one BILAG A score and/or ≥ 2 BILAG B scores.

CCI [redacted]

14.3 Secondary Estimands

The analysis of secondary estimands will be performed at final analyses of Cohort A and Cohort B (where applicable).

14.3.1 Change from Baseline in CLA-IGA Score at Week 16 and Week 24

The cutaneous lupus activity Investigator's global assessment (CLA-IGA) is a 5-point score that defines the level of disease severity based on overall lesion characteristics where 0 is "clear" and "4" is severe.

Attributes of the estimand are described in the table below.

Endpoint(s)	• Change from baseline in CLA-IGA at Week 16 • Change from baseline in CLA-IGA at Week 24
Population(s)	• Cohort A • Cohort B with CLASI-A ≥ 8 at Screening and confirmed at Day 1
Treatment	Enpatoran vs placebo
[redacted]	[redacted]
Population-level summary measure	Mean difference between study intervention groups

Descriptive Analysis

The CLA-IGA score will be summarized as an ordered categorical variable (providing counts and percentage of participants) and as a continuous variable at Baseline and each on-treatment scheduled visit. A table of the CLA-IGA score counts at baseline vs score at week 16 and similarly at week 24 will be presented by study intervention group to illustrate the shift in score from Baseline. Additionally, a bar chart presenting the proportion improved and worsened at each on-treatment visit grouped by study intervention group will be provided.

Inferential Analysis

A MMRM will be fitted to model the change from Baseline in CLA-IGA with study intervention group, analysis visit, treatment by analysis visit interaction as categorical variables, stratification factors (see Section 14), and baseline CLA-IGA as a continuous variable. An unstructured correlation pattern will be used to estimate the variance-covariance of the within-subject repeated measures. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Should the model fail to converge (including problems in estimating final Hessian matrix), then:

- A different structure for the variance-covariance matrix will be tested in the following order: Toeplitz, autoregressive (1), compound symmetry.
- In addition, the sandwich estimator of the standard error of the fixed effects parameters will be used as it can produce statistical inference more robust to variance-covariance pattern misspecification. In this alternative model, the between-within method will be used to estimate the denominator degrees of freedom.

This model assumes missing data are MAR.

The analysis will be conducted using all changes from Baseline in CLA-IGA observed up to Week 24 visit (see Section 9.7 for time windowing) in accordance with the treatment policy strategy for handling the intercurrent events. LS means for change from Baseline in CLA-IGA together with its 95% CIs will be presented by study intervention group and analysis visit, in a tabular and graphical form. The difference in the LS means between each study intervention group and placebo together with accompanying two-sided 95% CI will also be tabulated.

Cumulative distribution function for change score from Baseline at the visit of interest will be displayed by study intervention group to depict the treatment effect across the population.

14.3.2 Change in PGA of Cutaneous Lupus Disease Activity at Week 16 and Week 24

The physician's global assessment of cutaneous lupus disease activity is used to quantify disease activity and is measured using a 100 mm visual analog scale where 0 is "no cutaneous lupus disease activity" and 100 is "maximum cutaneous lupus disease activity". On a first version of the questionnaire, the length of the scale was 101.8 mm. All assessments collected from this incorrect version will then be corrected applying the following factor: *100/101.8. The corrected score will then be expressed on a 0-100 mm scale.

Attributes of the estimand are described in the table below.

Endpoint(s)	• Change from baseline in Physician's Global Assessment of Cutaneous Lupus Disease Activity at Week 16 • Change from baseline in Physician's Global Assessment of Cutaneous Lupus Disease Activity at Week 24
Population(s)	• Cohort A • Cohort B with CLASI-A ≥ 8 at Screening and confirmed at Day 1
Treatment	Enpatoran vs placebo
[redacted]	[redacted]
Population-level summary measure	Mean difference between study intervention groups

Descriptive Analysis

PGA of cutaneous lupus disease activity and change score from Baseline will be summarized using standard statistics at Baseline and each on-treatment scheduled visit. A scatter plot of baseline values vs values at Weeks 16 and 24 by study intervention group will be presented for visualization purposes with the diagonal reference line (y=x) to be able to see potential shift.

Inferential Analysis

The same analysis as described for CLA-IGA in section 14.3.1 will be conducted: a MMRM will be fitted to model the change from Baseline in PGA of cutaneous lupus disease activity with study intervention group, analysis visit, treatment by analysis visit interaction as categorical variables, stratification factors (see Section 14), and baseline PGA of cutaneous lupus disease activity as a continuous covariate.

14.3.3 Clinically Meaningful CS Reduction by Week 12 and Sustained through Week 24

Analyses described in this section will be performed at the final analysis.

Attributes of the estimands are described in the table below:

Endpoint	Clinically meaningful CS reduction, defined as reduction of daily prednisone-equivalent dose from ≥ 10 mg at Day 1 to ≤ 5 mg by the Week 12 visit and sustained through Week 24
Population(s)	• SLE participants (Cohort B) with daily prednisone-equivalent dose ≥ 10 mg at Day 1 • Cohort A participants with daily prednisone-equivalent dose ≥ 10 mg at Day 1
Treatment	Enpatoran vs placebo
[redacted]	[redacted]
Population-level summary measure	Odds ratio (conditional on stratification factors) between each active dose and placebo

Clinically meaningful CS reduction at Week 12 will be assessed based on the "CORTICOSTEROID MEDICATION DETAILS" form. Sustainment of the reduction will be assessed throughout the period between Week 12 and Week 24 (see appendix 18.2 for derivation of daily prednisone-equivalent dose).

A composite estimand strategy will be applied to handle the intercurrent events. Participants who experience any of these intercurrent events will be considered as not achieving CS reduction.

Descriptive Analysis

The number and percentage of participants with a clinically meaningful CS reduction will be provided.

Inferential Analysis

A logistic regression of clinically meaningful CS reduction status (yes/no) on the study intervention groups as a categorical variable and the stratification factors (see Section 14) will be fitted.

Odds ratios together with their 95% CI will be provided for each enpatoran group vs placebo. Treatment effect (and 95% CI) on the probability scale will also be provided.

14.3.4 BICLA Response and Clinically Meaningful CS Reduction

This estimand will be analyzed at the final analysis. Its attributes are described in the table below:

Endpoint	BICLA response and clinically meaningful CS reduction, defined as reduction of daily prednisone-equivalent dose from ≥ 10 mg at Day 1 to ≤ 5 mg by the Week 12 visit and sustained through Week 24
Population(s)	SLE participants (Cohort B) with daily prednisone-equivalent dose ≥ 10 mg at Day 1
Treatment	Enpatoran vs placebo
[redacted]	[redacted]

Population-level summary measure	Odds ratio (conditional on stratification factors) between each active dose and placebo

A composite estimand strategy will be applied to handle the intercurrent events. Participants who experience any of these intercurrent events will be considered as non-responder.

Participants will be considered as responders if they have a BICLA response at Week 24 and a clinically meaningful CS reduction from ≥ 10 mg at Day 1 to ≤ 5 mg by the Week 12 visit sustained through Week 24 was observed (see section 14.3.3). If BICLA response is missing at Week 24, it will be considered as a non-response (see Section 14.2.1).

Descriptive Analysis

The number and percentage of participants with a BICLA response and a clinically meaningful CS reduction will be provided.

Inferential Analysis

A logistic regression of the BICLA response and clinically meaningful CS reduction status (yes/no) on the study intervention groups as a categorical variable and the stratification factors will be fitted.

Odds ratios together with their 95% CI will be provided for each enpatoran group vs placebo. Treatment effect (and 95% CI) on the probability scale will also be provided.

14.3.5 CLA-IGA 0 or 1 at Week 16 and Week 24

Estimands attributes are described in the table below.

Endpoint(s)	• Occurrence of CLA-IGA 0 or 1 at Week 16 • Occurrence of CLA-IGA 0 or 1 at Week 24
Population(s)	• Cohort A • Cohort B with CLASI-A ≥ 8 at Screening and confirmed at Day 1
Treatment	Enpatoran vs placebo
[redacted]	[redacted]
Population-level summary measure	Odds ratio (conditional on stratification factors) between each active dose and placebo

Descriptive Analysis

The number and percentage of participants who have a CLA-IGA score of 0 or 1 (“clear” or “almost clear”) will be provided at each scheduled visit. Participants experiencing an intercurrent event prior to the visit of interest will be considered as not having a CLA-IGA score of 0 or 1. A line plot depicting the percentage of responders over time grouped by study intervention group will also be provided.

Inferential Analysis

The same analysis as described in section 14.3.3 will be performed to assess the treatment effect on the occurrence of CLA-IGA 0 or 1 at Week 16 and Week 24.

Some CLA-IGA assessments have been conducted while Investigators were not trained. To assess the impact of the training on the results observed, descriptive and inferential analyses described in this section will be replicated using assessments collected on or after Investigator's training only.

14.3.6 SRI-4 Response through Week 24

This analysis will be conducted at the final analysis. Attributes of the estimand are described in the table below.

Endpoint	Systemic lupus erythematosus Responder Index-4 (SRI-4) response at Week 24
Population(s)	SLE participants (Cohort B)
Treatment	Enpatoran vs placebo
CCI	CCI
Population-level summary measure	Odds ratio (conditional on stratification factors) between each active dose and placebo

The systemic lupus erythematosus responder index-4 (SRI-4) response is a measure of reduced SLE disease activity. A participant is an SRI-4 responder at a given time-point if they achieve:

- CCI
- No worsening of ≥ 0.3 points in PGA of SLE disease activity score compared to Baseline (PGA score expressed on a 0 – 3 scale) AND
- No new BILAG A organ domain scores and ≤ 1 new BILAG B organ domain score compared to Baseline using BILAG 2004

CCI

Imputation of missing items will be performed for CCI, PGA of SLE disease activity and BILAG questionnaires as described in section 9.11. If SRI-4 response is still missing after imputation at a visit, the participant will be considered as a non-responder.

Descriptive Analysis

SRI-4 response will be summarized using descriptive statistics (frequency and percentage) at each on-treatment scheduled visit. The number and percentage of participants meeting each SRI-4 component

criterion will be provided during the on-treatment period. Additionally, a line plot depicting the percentage of responders over time grouped by study intervention group will also be provided.

Inferential analysis

A logistic regression of SRI-4 response at Week 24 on the study intervention groups as a categorical variable and the stratification factors will be conducted.

Odds ratio together with its 95% CI will be provided at Week 24 for each enpatoran group vs placebo. Treatment effect (and 95% CI) on the probability scale will also be provided. In addition, observed SRI-4 response (yes/no) will be summarized at each scheduled timepoint.

Subgroup analysis

Treatment effect in SRI-4 response will be assessed in subgroups CCI [redacted]

14.3.7 LLDAS Attainment through Week 24

This analysis will be conducted at the final analysis. Attributes of the estimand are described in the table below.

Endpoint	LLDAS attainment at Week 24
Population(s)	SLE participants (Cohort B)
Treatment	Enpatoran vs placebo
[redacted]	[redacted]
Population-level summary measure	Odds ratio (conditional on stratification factors) between each active dose and placebo

Lupus low disease activity state (LLDAS) is attained at a specific visit if the following criteria are met at the visit (Golder 2020):

- CCI [redacted]
  - Renal, central nervous system, cardio-pulmonary: all descriptors of the system should be absent at the visit
  - Vasculitis: vasculitis descriptor of musculoskeletal system should be absent
  - Fever: fever descriptor of constitutional system should be absent
- No new descriptors of lupus disease activity compared with the assessment of the previous analysis visit
  - CCI [redacted]
- PGA (scale 0 – 3) ≤ 1
- Daily prednisolone-equivalent dose ≤ 7.5 mg from the day after the previous visit until the day of the current visit (see appendix 18.2 for derivation of daily prednisone-equivalent dose). If the previous visit is missed, the daily prednisolone-equivalent dose should be below or equal to 7.5 mg from 27 days prior to the current visit until that visit.
- Standard maintenance dosages of immunosuppressive drugs and approved biological agents

  This criterion will not be specifically programmed but is covered via the handling of the intercurrent event "protocol-prohibited medications as determined by EAC".

A composite estimand strategy will be applied to handle the intercurrent events: participants who experience any of these intercurrent events will be considered as not attaining LLDAS at all subsequent analysis visits.

CCI [redacted]

Descriptive Analysis

LLDAS attainment will be summarized using descriptive statistics (frequency and percentage) at each on-treatment scheduled visit. Additionally, a line plot depicting the percentage of responders over time grouped by study intervention group will also be provided.

Inferential analysis

A logistic regression of LLDAS attainment (yes/no) at Week 24 on the study intervention groups as a categorical variable and the stratification factors will be fitted.

Odds ratios together with their 95% CI will be provided for each enpatoran group vs placebo. Treatment effect (and 95% CI) on the probability scale will also be provided.

14.3.8 Remission Attainment through Week 24

This analysis will be conducted at the final analysis. Attributes of the estimand are described in the table below.

Endpoint	Remission attainment at Week 24
Population(s)	SLE participants (Cohort B)
Treatment	Enpatoran vs placebo
[redacted]	[redacted]
Population-level summary measure	Odds ratio (conditional on stratification factors) between each active dose and placebo

Remission attainment per 2021 DORIS definition (Vollenhoven 2021) is defined at a specific visit as meeting the following criteria at the visit:

- CCI [redacted]
- PGA of SLE < 0.5 (0-3 scale)
- Daily prednisolone-equivalent dose ≤ 5 mg from the day after the previous visit until the day of the current visit (see appendix 18.2 for derivation of daily prednisone-equivalent dose). If the previous visit is missed, the daily prednisolone-equivalent dose should be below or equal to 5 mg from 27 days prior to the current visit until that visit.
- Stable immunosuppressives including biologics

  This criterion will not be specifically programmed but is covered via the handling of the intercurrent event "protocol-prohibited medications as determined by EAC".

CCI [redacted]

Imputation for CCI [redacted] is described in section 9.11.2 and section 9.11.4 respectively. If at least one criterion for remission is not evaluable at a visit, remission will be considered as non-attained at the visit.

Descriptive Analysis

Remission attainment will be summarized using descriptive statistics (frequency and percentage) at each on-treatment scheduled visit. Additionally, a line plot depicting the percentage of responders over time grouped by study intervention group will also be provided.

Inferential analysis

A logistic regression of remission attainment (yes/no) on the study intervention groups as a categorical variable and the stratification factors will be fitted.

Odds ratios together with their 95% CI will be provided for each enpatoran group vs placebo. Treatment effect (and 95% CI) on the probability scale will also be provided.

14.3.9 Change from Baseline in Tender and Swollen 28-joint Count through Week 24 – Cohort B

Attributes of the estimand are described in the table below. It will be analyzed at the final analysis.

Endpoint	Change in the number of joints which are tender and swollen in 28-joint count from Baseline at Week 24
Population(s)	SLE participants from Cohort B CCI [redacted]
Treatment	Enpatoran vs placebo
[redacted]	CCI [redacted]
Population-level summary measure	Mean difference between study intervention groups

CCI [redacted]

Descriptive Analysis

The following continuous variables will be summarized at Baseline and each on-treatment scheduled visit using descriptive statistics:

- Tender 28-joint count (raw and absolute change from Baseline)
- Swollen 28-joint count (raw and absolute change from Baseline)
- Tender and swollen 28-joint count (raw and absolute change from Baseline)

  Tender and swollen 28-joint count = count of joints which are both tender and swollen
- Number and percentage of participants who achieved ≥ 50 % reduction in baseline tender and swollen 28-joint count at each scheduled on-treatment visit

Inferential Analysis

An MMRM will be fitted to model the change from Baseline in the tender and swollen 28-joint count (count of joints which are both tender and swollen) with study intervention group, analysis visit, treatment by analysis visit interaction, stratification factors, and baseline tender and swollen joint count as a continuous variable. An unstructured correlation pattern will be used to estimate the variance-covariance of the within-subject repeated measures. The Kenward-Roger method will be used to estimate the

denominator degrees of freedom. Should the model fail to converge (including problems in estimating final Hessian matrix), then:

- A different structure for the variance-covariance matrix will be tested in the following order: Toeplitz, autoregressive (1), compound symmetry.
- In addition, the sandwich estimator of the standard error of the fixed effects parameters will be used as it can produce statistical inference more robust to variance-covariance pattern misspecification. In this alternative model, the between-within method will be used to estimate the denominator degrees of freedom.

This model assumes missing data are MAR.

The analysis will be conducted using all changes from Baseline in tender and swollen joint count observed up to Week 24 analysis visit (see Section 9.7 for time windowing) in accordance with the treatment policy strategy for handling the intercurrent events. LS means for change from Baseline in tender and swollen joint count together with its 95% CIs will be presented by study intervention group and analysis visit, in a tabular and graphical form. The difference in the LS means between each study intervention group and placebo together with accompanying two-sided 95% CI will also be tabulated.

Cumulative distribution function for Week 24 change from Baseline will be displayed by study intervention group to depict the treatment effect across the population.

14.3.10 Change from Baseline in Physician's Global Assessment of SLE at Week 24

Attributes of the estimand are described in the table below. It will be analyzed at the final analysis.

Endpoint	Change from baseline in Physician's Global Assessment at Week 24
Population(s)	SLE participants from Cohort B
Treatment	Enpatoran vs placebo
[redacted]	[redacted]
Population-level summary measure	Mean difference between study intervention groups

PGA of SLE disease activity will be analyzed using the score converted on a 0-3 scale (see Section 9.11.4).

Descriptive Analysis

PGA of SLE and change from Baseline in PGA will be summarized using descriptive statistics at Baseline and each on-treatment scheduled visit.

Inferential Analysis

An MMRM as described in section 14.3.9 will be fitted. It will use study intervention group, analysis visit, treatment by analysis visit interaction, stratification factors, and baseline PGA as a continuous variable.

LS means for change from Baseline in PGA together with its 95% CIs will be presented by study intervention group and analysis visit, in a tabular and graphical form. The difference in the LS means between each study intervention group and placebo together with accompanying two-sided 95% CI will also be tabulated.

Cumulative distribution function for Week 24 change from Baseline will be displayed by study intervention group to depict the treatment effect across the population.

14.3.11 Time to First Moderate/Severe BILAG Flare from Day 1 through Week 24

Attributes of the estimand are described in the table below.

Endpoint	Time to first moderate/severe BILAG flare from Day 1 through Week 24
Population(s)	SLE participants from Cohort B
Treatment	Enpatoran vs placebo
[redacted]	[redacted]
Population-level summary measure	Hazard ratio (conditional on stratification factors) between each active dose and placebo

A moderate flare is defined as at least two BILAG B organ scores due to items that are new or worse* in the month leading up to the current visit, when the participant does not meet the criteria for the severe flare.

A severe flare is defined as at least one BILAG A score in any organ systems due to one or more items that are new or worse*, in the month leading up to the current visit, compared to the participant's condition during the previous month.

*"Items that are new or worse" means that if the assigned grade A/B or C contains any item which is WORSE or NEW, such grade will be included into the flare consideration. This is valid for clinical organ domains. For laboratory organ domains (i.e., renal and hematological) where items are not classified as worse or new, there has to be an increase in score from B to A or C to B for flare to be considered.

All post-baseline BILAG assessments until Week 24 will be considered.

Time to first moderate/severe BILAG flare (weeks) will be derived as follows:

$$Time\ to\ first\ moderate/severe\ BILAG\ flare = [min(Dates\ of\ visit\ with\ moderate/severe\ BILAG\ flare) - Date\ of\ randomization + 1]/7$$

The following censoring rules will be applied:

- Participants discontinuing the study prior to Week 24 without moderate/severe flare will have their time to first moderate/severe flare censored at the last visit at which flare could have been assessed (i.e., date of last BILAG assessment). Participants discontinuing the study prior to any post-baseline assessments will be censored at randomization date.
- Participants completing the 24-week treatment period without moderate/severe flare will have their time to first moderate/severe flare censored at Week 24.

The treatment effect on time to first moderate/severe flare will be estimated using a Cox's proportional hazard model with study intervention group as main effect and stratified by baseline CCI [redacted] total score from eCRF CCI [redacted] CCI [redacted] at Screening and region from IWRS). The hazard ratio (HR) together with its 95% CI will be provided.

Each stratum will define a separate baseline hazard function, i.e., for the i-th stratum the hazard function is expressed as: $h(i;t) = h(i,0;t) \exp(x\beta)$, where $h(i,0;t)$ defines the baseline hazard function for the i-th stratum and x defines the study intervention group and β is the unknown regression parameter. Ties will be handled by replacing the proportional hazards model by the discrete logistic model.

The one-sided p-value from the stratified log rank test will be reported. This p-value should be considered as exploratory.

Results from an unstratified analysis will also be provided (HR together with its 95% CI and one-sided p-value from log rank test).

Kaplan-Meier estimates (product-limit estimates) for the time to first moderate/severe flare will also be provided by study intervention group together with a summary of associated statistics (median, Q1 and Q3, minimum and maximum) including the corresponding two-sided 95% CI of the median (calculated according to Brookmeyer and Crowley). Rates of participants with moderate/severe BILAG flare together with their 95% CI (using the log-log transformation according to Kalbfleisch and Prentice) will be provided at each on-treatment scheduled visit. The estimate of the standard error will be computed using Greenwood's formula. In addition, the number of participants with at least one event (overall and by flare severity) will be presented.

Cumulative distribution function estimated using Kaplan-Meier method will be displayed by study intervention group.

14.3.12 Time to First SFI Severe Flare from Day 1 through Week 24

Attributes of the estimand are described in the table below. It will be produced for the final analysis.

Endpoint	Time to first SFI severe flare from Day 1 through Week 24

Population(s)	SLE participants from Cohort B
Treatment	Enpatoran vs placebo
[redacted]	[redacted]
Population-level summary measure	Hazard ratio (conditional on stratification factors) between each active dose and placebo

[redacted]

Mild or moderate flare is defined as meeting any of the criteria below:

- Change in [redacted] score ≥ 3 (but no more than 12)
- New or worsening disease activity in:
  - [redacted]
  - Nasopharyngeal ulcers AND/OR
  - Pleuritis AND/OR
  - Pericarditis AND/OR
  - Arthritis AND/OR
  - Fever (SLE)
- Increase in prednisone, but not to > 0.5 mg/kg/day
- Added NSAID or hydroxychloroquine for SLE activity
- ≥ 1.0 increase in PGA score, but not to more than 2.5

Severe flare is defined as meeting any of the criteria below:

- Change in [redacted] score > 12
- New or worsening disease activity in:
  - [redacted]
  - Nephritis AND/OR
  - Myositis AND/OR
  - Platelets < 60,000 AND/OR
  - Hemolytic anemia: Hb < 70 g/L or decrease in Hb > 30 g/L
- Increase in prednisone to > 0.5 mg/kg/day for any kind of flare
- New cyclophosphamide, azathioprine, methotrexate for SLE activity

- Hospitalization for SLE activity
- Increase in PGA score to > 2.5

Since some laboratory components of the CCI [redacted] will be blinded during the study, the eCRF item related to the change in CCI [redacted] cannot be used. Hence, change in CCI [redacted] will be derived using the actual total score (tick boxes 'Change in CCI [redacted] instrument score of 3 points or more [but not to more than 12]' and 'Change in CCI [redacted] instrument score to greater than 12' in eCRF will not be considered).

Time to first SFI severe flare (weeks) will be derived as follows:

$$Time\ to\ first\ SFI\ severe\ flare\ =\ [min(Dates\ of\ visit\ with\ SFI\ severe\ flare) - Date\ of\ randomization + 1]/7$$

The following censoring rules will be applied:

- Participants discontinuing the study prior to Week 24 without SFI severe flare will have their time to first SFI severe flare censored at the last visit at which flare could have been assessed (i.e., date of last SFI assessment). Participants discontinuing the study prior to any post-baseline assessments will be censored at randomization date.
- Participants completing the 24-week treatment period without SFI severe flare will have their time to first moderate/severe flare censored at Week 24.

The same analysis as described for time to first moderate/severe BILAG flare (section 14.3.11) will be performed.

14.3.13 Change from Baseline in Skindex-29+3 Scores at Week 24

Attributes of the estimands related to Skindex-29+3 domain scores are described in the table below.

Endpoint(s)	• Change from Baseline in Skindex-29+3 symptom domain score at Week 24 • Change from Baseline in Skindex-29+3 functioning domain score at Week 24 • Change from Baseline in Skindex-29+3 emotion domain score at Week 24 • Change from Baseline in Skindex-29+3 lupus-specific domain score at Week 24
Population(s)	Participants with a baseline Skindex-29+3 and at least one post-baseline Skindex-29+3 score in: • Cohort A • Cohort B with CLASI-A ≥ 8 at Screening and confirmed at Day 1
Treatment	Enpatoran vs placebo
[redacted]	CCI [redacted]
Population-level summary measure	Model LS mean difference between study intervention groups

Descriptive Analysis

Symptom, functioning, emotion domain scores and their changes from Baseline will be summarized using descriptive statistics at Baseline and each on-treatment scheduled visit.

A boxplot displaying the raw score by scheduled visit will be provided for each domain.

Inferential Analysis

For each scale, an MMRM as described in section 14.3.9 will be fitted. It will include the change in score from baseline as the dependent variable, study intervention group, analysis visit, treatment by analysis visit interaction as categorical variables, stratification factors (see Section 14), and baseline score as a continuous variable will be fitted. The model will include data until Week 24 visit.

LS means for change from Baseline in each score together with its 95% CIs will be presented by study intervention group and analysis visit, in a tabular and graphical form. The difference in the LS means between each study intervention group and placebo together with accompanying two-sided 95% CI will also be tabulated.

Empirical cumulative distribution function (eCDF) for Week 24 change from Baseline will be displayed by study intervention group to depict the treatment effect across the population.

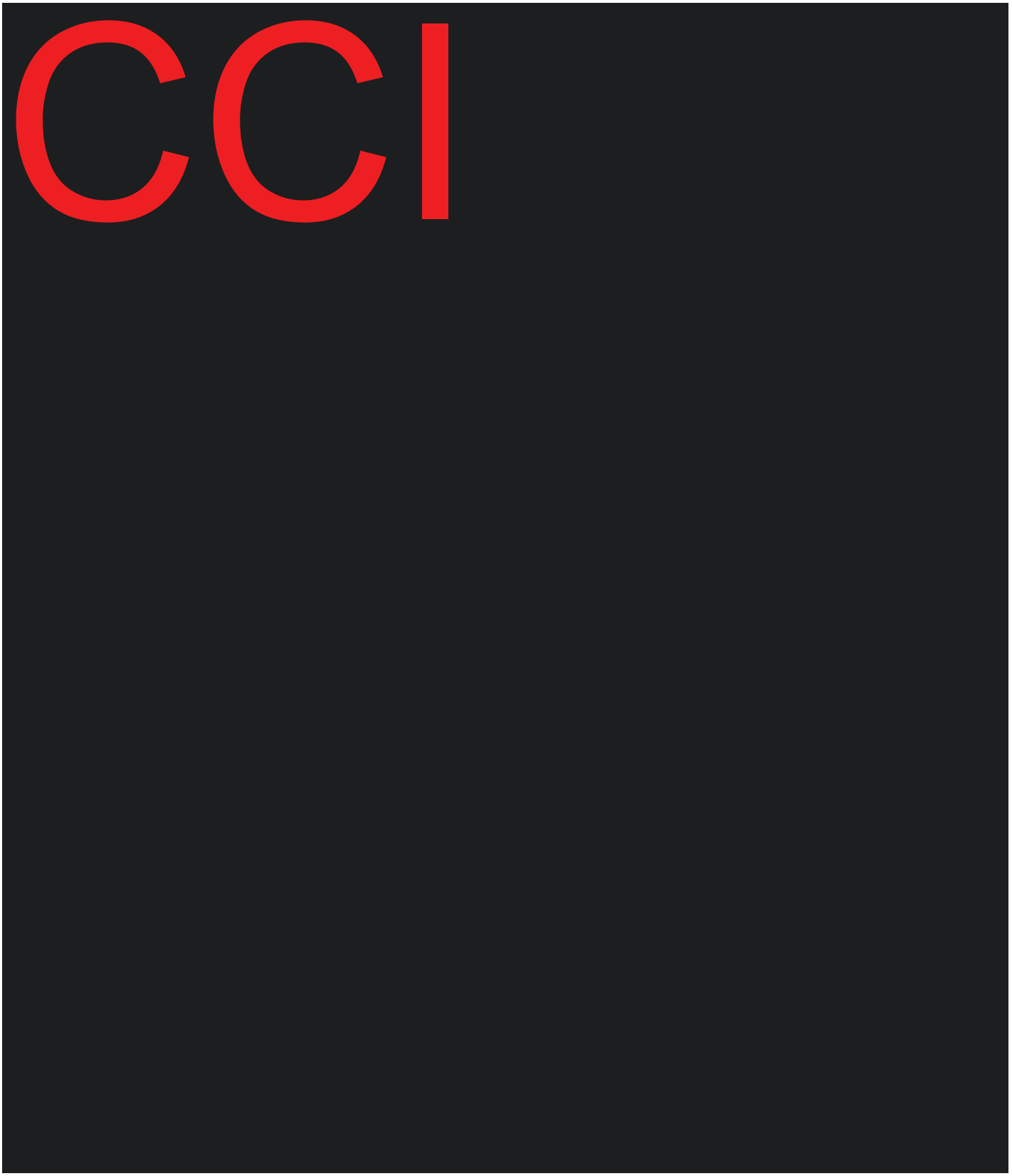
14.3.14 Change from Baseline in FACIT-Fatigue Score at Week 24

Attributes of the estimand are described in the table below.

Endpoint	Change from Baseline in FACIT-Fatigue score at Week 24
Population(s)	Participants with a baseline FACIT-Fatigue score and at least one post-baseline FACIT-Fatigue score in: • Cohort A • Cohort B
Treatment	Enpatoran vs placebo
[redacted]	[redacted]
Population-level summary measure	Model LS mean difference between study intervention groups

The same analysis as described for change from Baseline in Skindex-29+3 scores (see section 14.3.13) will be conducted (same outputs will be provided).

CCI [redacted]


CCI

CCI

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

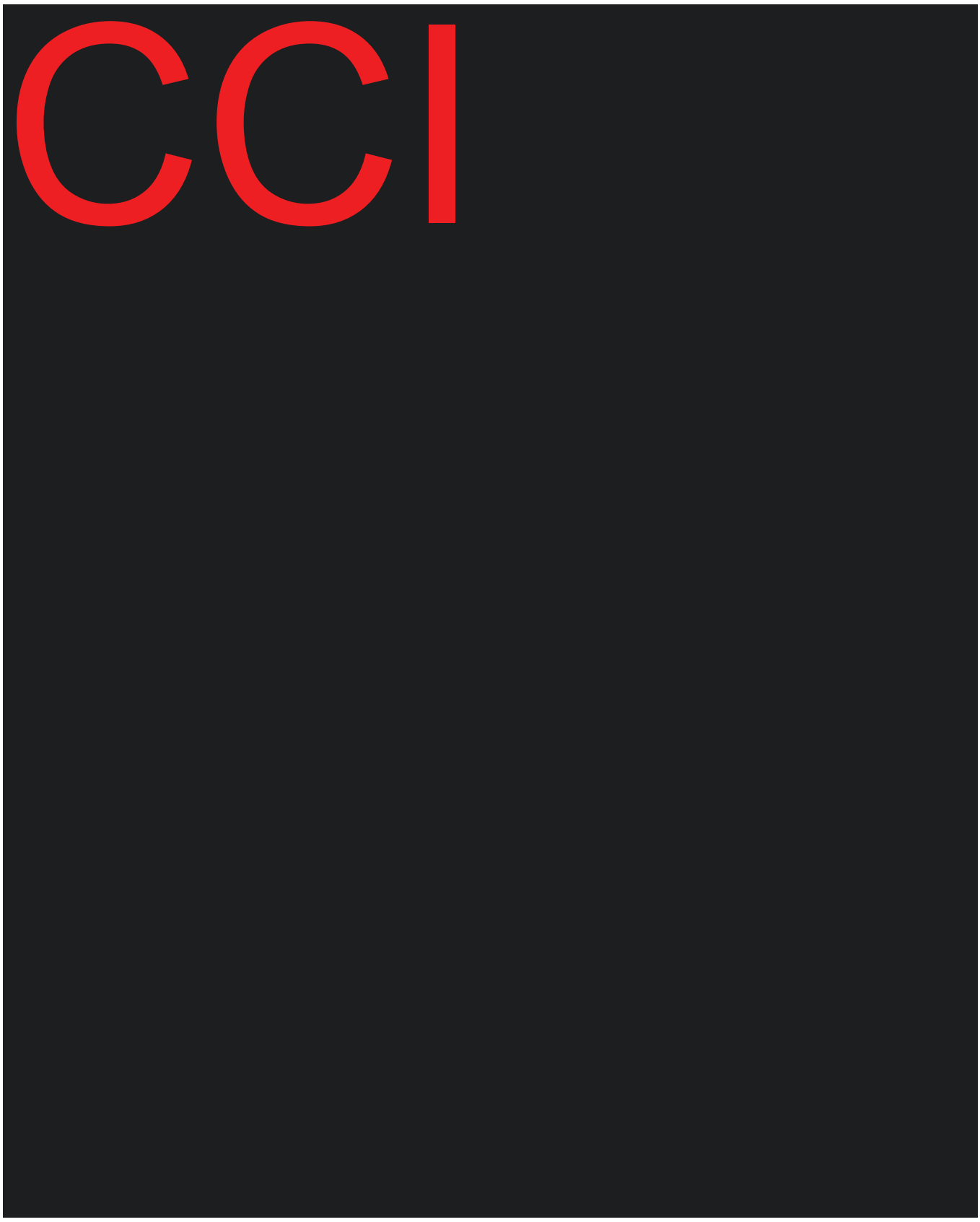
[redacted]

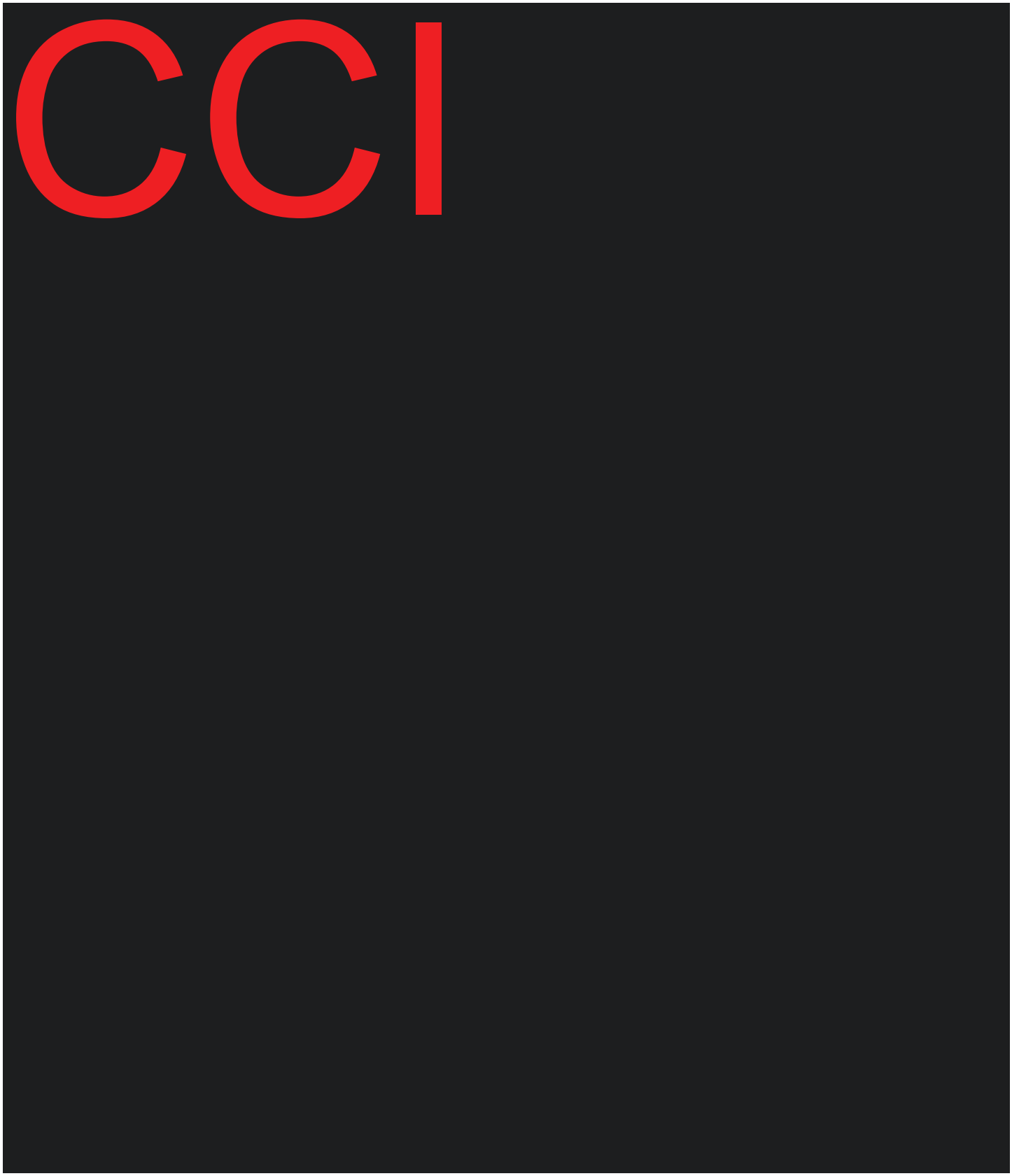
[redacted]

[redacted]

CCI [redacted]

- [redacted]
- [redacted]
- [redacted]


CCI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15 Safety Analyses

Safety analyses will be performed according to the as-treated principle on the safety analysis set by cohort and study intervention group unless otherwise specified. These will be conducted at final analyses of Cohort A and Cohort B. The analyses planned for the primary analysis of Cohort A are identified with an asterisk (*).

15.1 Adverse Events

Treatment-emergent adverse events (TEAE) are those events with onset or worsening dates occurring on or after the first dose of study intervention.

This also includes AEs ongoing at Baseline, which first improve under study intervention and then worsen irrespective of baseline. Adverse events with changes in toxicity grade, seriousness or outcome of AEs are recorded as separate entries in the eCRF with associated end and start dates (start date equals end date of previous entry, supported in eCRF v8.4 by "AECHGID" in SUPPAE). Records of the same AE will be considered as one event in the analysis. If the severity or seriousness of the reported event worsens after start of treatment, the TEAE flag will be re-evaluated for the worse and the subsequent records as per the TEAE definition. These events will be kept as separate records in the database in order to maintain the full detailed history of the events. The overall outcome of the adverse event is the outcome of the last event in the sequence. When such AEs are listed, start, end date and outcome should be provided together with change date, toxicity grade and seriousness per episode.

Adverse events are considered as related to study intervention if their relationship with the study intervention is missing, unknown or yes.

Adverse events will be summarized using the latest version of MedDRA at the time of the database lock with PT as event category and MedDRA primary SOC body term as body system category.

Analysis by severity will be performed according to NCI-CTCAE version 5.0. In case a participant has events with missing and non-missing grades, the maximum of the non-missing grades will be used. No imputation of missing grades will be performed.

Incomplete AE-related dates will be handled as specified in section 9.10.

All analyses described in this section 15.1 will be based on TEAEs if not otherwise specified.

Unless otherwise specified, TEAEs will be summarized by number and percentage of participants with at least one TEAE in the category of interest, by study intervention group, primary SOC in alphabetical order, and PT in decreasing incidence overall.

Each participant will be counted only once within each SOC or PT. If a participant experiences more than one AE within a SOC or PT for the same summary period, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

The 3-tier approach to AE reporting will be applied.

15.1.1 All Adverse Events

Description of the Three-tier Analysis Approach

The 3-tier approach for summarizing and analyzing AEs in clinical studies will be followed. AEs in different tiers are analyzed using different types of statistical analysis.

Pre-specified AESI will be analyzed as part of Tier 1 if they fulfill the rule-of-4 (at least 4 participants in any of the study intervention groups). Otherwise, such AEs will be included in Tier 3. The pre-specified terms considered for Tier 1 are (see section 15.2.3 for further details):

- Severe infections NCI-CTCAE grade ≥ 3 and all-related PTs
- CCI [redacted]
- [redacted]
- [redacted]

All of these prespecified events will be summarized in a table. Incidence rate and difference in incidence rate between each active group and placebo will be provided. A 95% CI for the difference in incidence rate will be provided for prespecified events fulfilling the rule-of-4 only. CI will be estimated using Miettinen & Nurminen method.

All TEAEs (unique preferred terms) will be classified as belonging to Tier 2 or Tier 3 and summarized in a table. Incidence rate and difference in incidence rate between each active group and placebo will be provided. A 95% CI for the difference in incidence rate will be provided for adverse events fulfilling the rule-of-4 only. CI will be estimated using Miettinen & Nurminen method.

Only TEAEs with at least one study intervention group with incidence proportion ≥ 5% will be presented in the body of the CSR.

Statistical Outputs

The following tables will be provided:

- Overview of TEAEs including (*):
  - TEAEs
  - TEAEs, Grade ≥ 2, Grade ≥ 3, Grade ≥ 4
  - Related TEAEs

- Related TEAEs, Grade ≥ 2, Grade ≥ 3, Grade ≥ 4
- Serious TEAEs
- Non-serious TEAEs
- Related Serious TEAEs
- TEAEs leading to death
- Related TEAEs leading to death

- Prespecified Tier 1/3 TEAEs (displayed by term including incidences, risk differences and respective confidence limits for the difference in group incidence proportions, as applicable according to rule-of-4) as described above per the 3-tier analysis approach (see description of the 3-tier approach above)
- Tier 2 and Tier 3 TEAEs (displayed by PT including incidences, risk differences and respective confidence limits for the difference in group incidence proportions, as applicable according to Rule-of-4) as described above in the 3-tier analysis approach (see description of the 3-tier approach above)
- TEAEs by SOC and PT (*)
- TEAEs by SOC and PT and worst grade (Any Grade, Grade ≥ 2, Grade ≥ 3, Grade ≥ 4) (*)
- Related TEAEs by SOC and PT (*)
- TEAEs excluding SAEs, with frequency ≥ 5% in any study intervention group by SOC and PT. "Number of subjects with at least one event" represents the number of participants with at least one AE among AEs where frequency is ≥ 5% in at least one study intervention group.

For Tier 1 and Tier 2 events each, a forest plot displaying incidence rates, differences in incidence rates as well as the CI for the difference will be provided.

The overview of TEAEs will also be provided in the population of CLE participants from Cohort A.

A listing of all AEs will be provided.

15.1.2 Adverse Events Leading to Discontinuation of Study Intervention

The overall summary of AEs leading to discontinuation of study intervention will include the frequency (number and percentage) of participants with each of the following, split by cohort and study intervention group:

- TEAEs leading to permanent discontinuation (drug withdrawn)
- Related TEAEs leading to permanent discontinuation (drug withdrawn)
- TEAEs leading to temporary discontinuation (drug interrupted)
- Related TEAEs leading to temporary discontinuation (drug interrupted)

A frequency table of TEAE leading to permanent discontinuation of study intervention will also be provided by primary SOC in alphabetical order and, within SOC, sorted by PT in decreasing incidence overall.

15.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

15.2.1 Deaths

Death date and reason for death are collected on the "DEATH" CRF form.

A participant data listing including date and reason of death, PT of AEs with fatal outcome together with selected dosing information (date of first/last administration) will be provided.

15.2.2 Serious Adverse Events

The following frequency tables will be prepared for serious TEAEs:

- Incidence of serious TEAEs by SOC and PT (*)
- Incidence of related serious TEAEs by SOC and PT (*)

A listing of SAEs will also be provided with the relevant information with a flag for SAEs with onset outside the on-treatment period.

15.2.3 Other Significant Adverse Events

The following events are defined as AE of Special Interest (AESI) as per protocol and will be included in Tier 1:

- Severe infections NCI-CTCAE grade ≥ 3
- CCI [redacted]
- [redacted]
- [redacted]

AESI will be identified using the corresponding flag entered in the "Adverse Event" eCRF page. In order to define the category to which they belong, SMQs or primary SOC will be used depending on the AESI (see table below).

Details of derivation for AESI categories are explained below:

AESI categories	Derivation
Severe infections	Primary SOC = 'Infections and Infestations' - Severe events only (i.e., ≥ Grade 3)
CCI [redacted]	[redacted]

AESI will be summarized as part of the 3-tier approach described in section 15.1.1 at primary analysis of Cohort A and final analyses of Cohort A and Cohort B.

15.3 Clinical Laboratory Evaluation

All laboratory values will be reported in SI units. Time window will be applied to laboratory assessments (see section 9.7).

Laboratory values (including corresponding normal ranges) from the central laboratory will be used for summary statistics and shift tables.

In case both central and local labs are collected, summary statistics will be based on central lab collected data, while summaries of worst on-treatment abnormalities will be based on both local and central lab data.

Laboratory results will be graded according to NCI-CTCAE version 5.0. Laboratory parameters which cannot be graded per NCI-CTCAE will be presented according to the categories: below normal limit, within normal limits and above normal limit (according to the laboratory normal ranges).

The definition of baseline measurement is provided in section 9.2.

Values below the detection limit will be imputed by half of the detection limit. If a text value with an "> x" is reported it will be analyzed as +1 significant digit, e.g., "> 7.2 mmol" will be analyzed as 7.3.

Quantitative data (hematology, biochemistry, coagulation and urinalysis) will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) of raw values and absolute changes from baseline at each on-treatment scheduled visit.

Qualitative data (hematology, biochemistry and coagulation) based on reference ranges will be described according to the categories (i.e., low, normal, high). For urinalysis parameters, the classification Normal, Trace/+, ++, +++, ++++ will be used instead.

Abnormalities classified according to NCI-CTCAE toxicity grading version 5.0 will be described using the worst on-treatment grade. Unless otherwise specified, number of participants with missing measurements will be presented as separate category. For those parameters which are graded with two directions of toxicities such as potassium (hypokalemia/hyperkalemia), the toxicities will be summarized

separately. Low direction toxicity (e.g., hypokalemia) grades at Baseline and post-baseline will be set to 0 when the variables are derived for summarizing high direction toxicity (e.g., hyperkalemia), and vice versa. The same applies for non-gradable parameter, and description of changes from Normal/Low to High and Normal/High to Low will be provided, accordingly. The direction of parameters can be found in the MS ADaM template, except for eGFR for which the worst post-baseline value will be considered as the lowest value, and CO_2 for which the worst post-baseline value will be considered in the two directions (both lowest and highest values).

For **WBC differential counts** (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts), the absolute value will be used when reported. When only percentages are available (this is mainly important for neutrophils and lymphocytes, because the CTCAE grading is based on the absolute counts), the absolute value is derived as follows:

Derived differential absolute count = (WBC count) * (Differential % value / 100)

If the range for the differential absolute count is not available (only range for value in % is available) then Grade 1 will be attributed to as follows:

- Lymphocyte count decreased:

  derived absolute count does not meet Grade 2-4 criteria, and

  % value < % LLN value, and

  derived absolute count ≥ 800/mm^3
- Neutrophil count decreased

  derived absolute count does not meet Grade 2-4 criteria, and

  % value < % LLN value, and

  derived absolute count ≥ 1500/mm^3

For **calcium**, CTCAE grading is based on Corrected Calcium and Ionized Calcium (CALCIO), if available. Corrected Calcium is calculated from Albumin and Calcium as follows

Corrected calcium (mmol/L) = measured total calcium (mmol/L) + 0.02 (40 - serum albumin [g/L])

Liver function tests: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin are used to assess possible drug induced liver toxicity. The ratios of test result over upper limit of normal (ULN) will be calculated and classified for these three parameters during the on-treatment period.

Summary of liver function tests will include the categories listed below. The number and percentage of participants with each of the following during the on-treatment period will be summarized by study intervention group:

- ALT ≥ 3×ULN, ALT ≥ 5×ULN, ALT ≥ 10×ULN, ALT ≥ 20×ULN
- AST ≥ 3×ULN, AST ≥ 5×ULN, AST ≥ 10×ULN, AST ≥ 20×ULN

- (ALT or AST) ≥ 3×ULN, (ALT or AST) ≥ 5×ULN, (ALT or AST) ≥ 10×ULN, (ALT or AST) ≥ 20×ULN
- TBILI ≥ 2×ULN
- Concurrent ALT ≥ 3×ULN and TBILI ≥ 2×ULN (*)
- Concurrent AST ≥ 3×ULN and TBILI ≥ 2×ULN (*)
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN (*)
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and ALP > 2×ULN (*)
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and ALP ≤ 2×ULN or missing (*)

Concurrent measurements are those occurring on the same date.

Categories will be cumulative, i.e., a participant with an elevation of AST ≥ 10×ULN will also appear in the categories ≥ 5×ULN and ≥ 3×ULN. Liver function elevation and possible Hy's Law cases will be summarized using frequency and percentage.

An evaluation of drug-induced serious hepatotoxicity (eDISH) plot will also be created, with different symbols for different study intervention groups, by graphically displaying two figures with log-scale transformed axes presented as:

- Peak serum ALT (/ULN) vs peak total bilirubin (/ULN) during the on-treatment period including reference lines at ALT = 3×ULN and total bilirubin = 2×ULN
- Peak serum AST (/ULN) vs peak total bilirubin (/ULN) during the on-treatment period including reference lines at AST = 3×ULN and total bilirubin = 2×ULN

In addition, a listing of all TBILI, ALT, AST and ALP values for participants with a post-baseline TBILI ≥ 2×ULN, ALT ≥ 3×ULN or AST ≥ 3×ULN will be provided.

Analysis for Parameters with NCI-CTCAE Grade Available

The laboratory toxicities will be tabulated using descriptive statistics (number of participants and percentages) during the on-treatment period. Grade 0 is not defined per NCI-CTCAE but will be used in derivations for simplicity to indicate that evaluable measurements are available. Laboratory values within normal range but considered grade 1 according to NCI-CTCAE will not be graded 1 (Grade 0, instead).

- A summary table of laboratory parameters (excluding amylase) by NCI-CTCAE grade will include number and percentage of participants with at least one value of Grade ≥ 0, Grade ≥ 3, Grade ≥ 4 during the on-treatment period.
- A shift table will summarize baseline NCI-CTCAE grade versus the worst on-treatment NCI-CTCAE grade (excluding amylase). The highest NCI-CTCAE grade during the on-treatment period is considered as the worst grade for the summary. (*)

  In case of gradings involving baseline measurements (parameters identified with a start [*] below) for the identification of grades during the on-treatment period, the shift table will present baseline normal and abnormal. Normal will include measurements below and within normal range (direction

increase), or measurements within and above normal range (direction decrease). In case of missing baseline values, the on-treatment grades will be generated assuming the baseline was normal.

The above analyses apply to hematology and chemistry evaluations which can be graded per NCI-CTCAE:

- Hematology

  Hemoglobin (HB) (anemia/ hemoglobin increased), Leukocytes (white blood cell decreased/ leukocytosis), Lymphocytes (lymphocyte count increased/decreased), Neutrophils / Absolute Neutrophils Count (ANC) (neutrophil count decreased), Platelet Count (PLT) (platelet count decreased), Eosinophils * (eosinophilia).

- Coagulation

  INR * (INR increased), Activated partial thromboplastin time (aPTT prolonged)

- Serum chemistry

  Albumin (hypoalbuminemia), Alkaline Phosphatase * (alkaline phosphatase increased), Alanine Aminotransferase * (ALT) (ALT increased), Aspartate Aminotransferase * (AST) (AST increased), Total Bilirubin * (blood bilirubin increased), Creatinine * (creatinine increased), Potassium (hypokalemia/ hyperkalemia), Sodium (hyponatremia/ hypernatremia), Calcium (hypocalcemia/hypercalcemia), Glucose (hypoglycemia), Gamma Glutamyl Transferase * (GGT) (GGT increased), eGFR (chronic kidney disease), Amylase (serum amylase increased), Lipase (lipase increased), Bicarbonate (blood bicarbonate decreased).

Analysis for Parameters with NCI-CTCAE Grade not Available

Hematology, chemistry (excluding amylase) and urinalysis evaluations which cannot be graded per NCI-CTCAE criteria will be summarized as frequency (number and row percentage) of participants as follows:

- Shifts from baseline normal to at least one result above normal during on-treatment period (*)
- Shifts from baseline normal to at least one result below normal during on-treatment period (*)

This applies to the following parameters:

- Hematology

  Hematocrit (low/high), Mean Corpuscular Hemoglobin (MCH) (low), Mean Corpuscular Volume (MCV) (low/high), monocytes (high), basophils (high), Erythrocyte Sedimentation Rate (ESR) (high)

- Coagulation

  Prothrombin time (low/high)

- Serum chemistry

  Chloride (low/high), Total Protein (low/high), Blood Urea Nitrogen (high), C-reactive Protein (CRP) (high)

- Urinalysis

pH (low [< 4.5]/high [≥ 9]), specific gravity (low [≤ 1.005]/high [≥ 1.030]), glucose (trace/1+, 2+, 3+, 4+), protein (trace/1+, 2+, 3+, 4+), occult blood (trace/1+, 2+, 3+, 4+), ketones (trace/1+, 2+, 3+, 4+), bilirubin (trace/1+, 2+, 3+, 4+), urobilinogen (trace/1+, 2+, 3+, 4+), nitrite (trace/1+, 2+, 3+, 4+), leukocyte esterase (trace/1+, 2+, 3+, 4+)

CCI [redacted]

Microscopic data (except UPCR), serum and urine pregnancy test results collected during the study will be listed.

The following figures will be provided for hematology, coagulation, serum chemistry (amylase excluded) parameters, CCI [redacted]

- Boxplots of the laboratory values (by study intervention group) by timepoint
- Boxplots of the change from baseline by timepoint

  Where applicable, reference lines for NCI-CTCAE grades should be added to graphical displays.

Listings of laboratory results will be provided for all laboratory parameters. The listings will be sorted by study intervention, parameter and assessment date or visit for each participant. Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges and NCI-CTCAE grades.

15.4 Vital Signs

Vital sign summaries will include all vital sign assessments from the on-treatment period. All vital sign assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing.

Time window will be applied to assessments of vital signs (see section 9.7).

The following vital sign parameters will be summarized using descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) for raw values and changes from baseline at each scheduled analysis visit:

- Body temperature (°C)
- Systolic and diastolic blood pressure (mmHg)
- Respiration rate (bpm)
- Pulse rate (beats/min)
- Weight (kg)

The maximum on-treatment changes of vital sign measurements from Baseline will be grouped as follows:

	Baseline Value	Change from Baseline

Body temperature increase	< 37 °C; 37 – < 38 °C; 38 – < 39 °C; 39 – < 40 °C; ≥ 40 °C	< 1 °C, 1 – < 2 °C, 2 – < 3 °C, ≥ 3 °C
Pulse rate increase from baseline	< 100 bpm; ≥ 100 bpm	≤ 20 bpm, > 20 – 40 bpm, > 40 bpm
Pulse rate decrease from baseline	< 100 bpm; ≥ 100 bpm	≤ 20 bpm, > 20 – 40 bpm, > 40 bpm
SBP increase from baseline	< 140 mmHg; ≥ 140 mmHg	≤ 20 mmHg, > 20 – 40 mmHg, > 40 mmHg
SBP decrease from baseline	< 140 mmHg; ≥ 140 mmHg,	≤ 20 mmHg, > 20 – 40 mmHg, > 40 mmHg
DBP increase from baseline	< 90 mmHg; ≥ 90 mmHg	≤ 20 mmHg, > 20 – 40 mmHg, > 40 mmHg
DBP decrease from baseline	< 90 mmHg; ≥ 90 mmHg,	≤ 20 mmHg, > 20 – 40 mmHg, > 40 mmHg
Respiration rate increase from baseline	< 20 bpm; ≥ 20 bpm	≤ 5 bpm, > 5 – 10 bpm, > 10 bpm
Respiration rate decrease from baseline	< 20 bpm; ≥ 20 bpm	≤ 5 bpm, > 5 – 10 bpm, > 10 bpm

SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure.

For each participant, the worst on-treatment value (i.e., lowest and highest when applicable) will be calculated. For the definition of baseline values, see section 9.2. Missing values will define a separate category.

The following summaries will be prepared for vital sign parameters as grouped above:

- Maximal shifts from baseline (changes in categories)

A participant data listing will present data for all vital signs. Worst on-treatment values (highest and/or lowest values depending on vital sign), and changes from Baseline in the highest categories as defined in the table above will be identified.

15.5 ECG Evaluations

ECG summaries will include all ECG assessments collected at Baseline and during the on-treatment period (Week 8, Week 20, Week 24 and ET). All ECG assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing.

The time windows below will be applied to allocate measurements to analysis visits. Unscheduled ECG measurements will be used for the analysis.

Analysis Visit	Target Day	Window Range
Day 1	1	1
Week 8 Day 57	57	> 1 – 70
Week 20 Day 141	141	71 – 154
Week 24 Day 169	169	≥ 155

The following analyses will be performed for each applicable ECG parameter (RR, PR, QRS, QT, ventricular rate -denoted as HR in what follows-, and QTcF) by cohort and study intervention group:

- Descriptive statistics at Baseline, at each post-baseline time point and changes from baseline at each post-baseline time point
- Frequency (number and percentage) of participants with notable ECG values according to the following categories by analysis visit and during the on-treatment period. (*)
    - HR < 50 bpm, < 40 bpm, < 30 bpm
    - HR increase from baseline > 20 bpm, > 30 bpm, > 40 bpm
    - HR decrease from baseline > 20 bpm, > 30 bpm, > 40 bpm
    - PR > 200 ms and > 220 ms
    - PR increase from baseline > 30 ms
    - QRS > 110 ms
    - QTcF > 450 ms, > 480 ms, > 500 ms
        - With/without concomitant antimalarial (ATC code level 3 = P01B)
    - QTcF increase from baseline > 30 ms, > 60 ms
        - With/without concomitant antimalarial (ATC code level 3 = P01B)

ECG interpretation (normal, abnormal/not clinically significant, abnormal/clinically significant) will be summarized at Baseline and during the on-treatment period.

A shift table from baseline to the worst on-treatment observation in ECG interpretation (normal, abnormal/not clinically significant, abnormal/clinically significant, missing and total) will also be provided.

Complete ECG profiles will be provided for participants with at least one notable ECG value or one notable ECG increase as defined above. For these participants, all ECG parameter values collected during the study will be provided.

15.6 Columbia-Suicide Severity Rating Scale

The Columbia-Suicide Severity Rating Scale (C-SSRS) assesses the suicidal behavior and suicidal ideation in participants. Abnormal findings identified via the C-SSRS will be recorded as AE.

Time window will be applied to assessments of C-SSRS (see section 9.7).

Occurrence of suicidal behavior is defined as having answered "yes" to a least 1 of the 4 suicidal behavior subcategories (actual attempt, interrupted attempt, aborted attempt, preparatory acts or behavior).

Occurrence of suicidal ideation is defined as having answered "yes" to at least 1 of the suicidal ideation sub-categories (wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with any methods [not plan] without intent to act, active suicidal ideation with some intent to act [without specific plan], and active suicidal ideation with specific plan and intent).

Occurrence of suicidality is defined as having at least 1 occurrence of suicidal ideation or at least 1 occurrence of suicidal behavior.

The number and percentage of participants with occurrence of suicidal behavior, occurrence of suicidal ideation and occurrence of suicidality will be summarized at Screening, Baseline and during the on-treatment period. Individual participant data listings will be also provided.

16 Analyses of Other Endpoints/Estimands

16.1 Pharmacokinetics

PK evaluation will be performed at final analyses of Cohort A and Cohort B.

All statistical analyses and descriptive summaries of PK data will be performed on the PKAS.

Blood samples for all study cohorts and parts will be collected for enpatoran determination according to the following schedule:

Table 5: Pharmacokinetic Sampling Times

Day	Time (h)	Time from Scheduled Sampling Allowed
Day 1 and Day 15	Predose	Within 60 minutes prior to morning dose administration
	Between 1-2	
	Between 4-6	
Day 29 (Week 4) and Day 85 (Week 12)	Predose	Within 60 minutes prior to morning dose administration
Day 57 (Week 8)	Predose	Within 60 minutes prior to morning dose administration
	Between 1-2	
Day 113 (Week 16), Day 141 (Week 20) and Day 169 (Week 24)	Any time postdose	

16.1.1 Descriptive Statistics of PK Concentration Data

PK concentrations will be descriptively summarized by cohort, part, scheduled visit, and time window using: number of subjects included in the analysis set (N), number of non-missing observations (n), percent of non-missing observations (n %), arithmetic mean (Mean), standard deviation (SD), geometric mean (GeoMean), the geometric coefficient of variation (GeoCV), and the 95% confidence interval for the GeoMean (lower confidence interval [LCI] 95% GM, upper confidence interval [UCI] 95% GM),

minimum (Min), median (Median), and maximum (Max). PK samples that are collected at any time postdose (Week 16, Week 20, and Week 24) will be summarized by scheduled visit.

Descriptive statistics will only be calculated for n > 2 in which a measurement of below the lower limit of quantification represents a valid measurement and will be taken as zero for summary statistics of PK concentration data. In case n ≤ 2, individual data will be presented (min, max) in summary tables. If the calculated mean or GeoMean is BLQ then it shall be reported in outputs as BLQ; SD, GeoCV% shall be reported as not determined (ND); LCI, UCI, Min, Median, and Max shall be reported as BLQ if applicable.

Descriptive statistics of PK concentration data will be calculated using values with the same precision as the source data and rounded for reporting purposes only. PK concentrations will be carried over with full precision as provided in the source data without any rounding applied to CDISC SDTM PC and ADaM PC domains.

The following conventions will be applied when reporting descriptive statistics of PK concentration data:

N, n:	0 decimal place
Mean, GeoMean, Min, Median, Max, SD, LCI 95% GeoMean, UCI 95% GeoMean:	3 significant digits
GeoCV:	1 decimal place

16.1.2 Descriptive Statistics of PK Parameter Data

PK parameter data will be descriptively summarized by cohort, part, and scheduled visit using: number of non-missing observations (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), minimum (Min), median (Median), maximum (Max), geometric mean (GeoMean), the geometric coefficient of variation (GeoCV) and the 95% confidence interval for the GeoMean (lower confidence interval [LCI] 95% GM, upper confidence interval [UCI] 95% GM).

Descriptive statistics will only be calculated for a PK parameter when n > 2. In case n ≤ 2, individual data will be presented (min, max) in summary tables.

PK parameters read directly from the measurements (i.e., C_{trough}) will be reported with the same precision as the source data. All other PK parameters will be reported to 3 significant figures. Descriptive statistics of PK parameter data will be calculated using full precision and rounded for reporting purposes only.

PK parameters will be provided with full precision, without any rounding applied to CDISC SDTM PP and ADaM PP domains.

The following conventions will be applied when reporting descriptive statistics of PK parameter data:

n	0 decimal place
Mean, Min, Median, Max, GeoMean, 95% CI, SD:	3 significant digits
CV%, GeoCV%:	1 decimal place

16.1.3 General Specifications for PK Concentration and PK Parameter Data

The following checks for enpatoran concentrations will be performed. This is not a comprehensive list and additional checks may be required.

- Samples will be flagged and removed from the analysis if they do not have actual time of PK sampling and actual time of prior/last dose recorded.
- Predose or trough samples which have been taken after the subsequent dosing will be reported as a protocol deviation. The resulting concentrations will be included in concentration listings but excluded from descriptive statistics of concentrations and from PK parameter estimation.
- If predose samples are collected outside of the hour prior to the morning dose administration, these will be excluded from the concentration summary and mean/median concentration plots.
- If the subject misses the last dose before the PK blood collection, the sample should be collected and presented in listings but flagged and excluded from the NCA analysis but not from Population PK analysis.
- Postdose samples that are collected outside specified time windows will be excluded from concentration summaries and mean/median concentration plots only for Weeks 1, 2 and 8.
- If an episode of vomiting occurs on the day of PK collection, the concentration results for that day will be flagged and identified in a listing. If it is known that the time of vomiting is after the time of enpatoran dosing, and prior to collection of a PK sample on the day of the PK collection, the concentration results following the time of vomiting will be excluded from the calculation of summary statistics.
- If a PK sample is collected outside of the blood collection window on days when there is a collection window specified in Table 1 Schedule of Assessments in the protocol (excluding Weeks 16, 20 and 24), the affected concentration results will be flagged and identified in a listing but will be excluded from NCA calculation and its summary statistics.

Values below the lower limit of quantification (BLQ) will be taken as zero for summary statistics of PK concentration data, PK parameter estimation (e.g., C_{trough}), and for graphical presentations.

Missing concentrations (e.g., no sample, insufficient sample volume for analysis, no result or result not valid) will be reported and used generally as "N.R.". A participant who withdraws prior to the last planned observation will be included in the analyses up to the time of discontinuation.

PK concentrations which are erroneous due to a sampling processing or analytical error (as documented in the bioanalytical report) may be excluded from the PK analysis if agreed by the Sponsor. In this case the rationale for exclusion will be provided in the CSR. Any other PK concentrations that appear implausible to the Clinical Pharmacologist/Clinical PK/PD Scientist will not be excluded from the analysis. Any implausible data will be documented in the CSR.

If other important protocol deviations occurred likely to affect the PK profile of participants, the impacted concentrations and PK parameters will be excluded from summary statistics and further statistical evaluation.

Any PK concentrations or PK parameters excluded from summary statistics will be included in participants listings and flagged; a reason for exclusion will be detailed in the CSR (e.g., a footnote or a table of exclusions). Any flags should be included in the study specific CDISC data sets.

PK concentrations and PK parameters excluded from summary statistics will not be included in mean/median figures. Mean/median plots will only contain values where $n > 2$. In case $\leq$ 2, individual participant profiles may be included in mean/median plots.

16.1.4 Estimation of Pharmacokinetic Parameters

The computer program Phoenix® WinNonlin® version 8.3, or higher (Certara, L.P., Princeton, New Jersey, USA) will be used to derive PK parameters applying non-compartmental analysis (NCA).

The statistical software SAS® (Statistical Analysis System, SAS-Institute, Cary NC, USA, windows version 9.1 or higher) may be used to generate additional PK parameters, produce tables, listings and figures.

16.1.4.1 Estimation of Pharmacokinetic Parameters in Plasma

In cases where actual dosing time is missing, scheduled time might be used for NCA after performance of adequate plausibility checks and agreement with the sponsor. Decision and rationale should be included in the CSR. There will be no imputation of missing data.

The following plasma PK parameter will be calculated where appropriate:

Symbol	Definition
C_{trough}	The concentration observed at the end of dosing interval immediately before next dosing

C_{trough}/Dose The dose normalized concentration observed at the end of dosing interval immediately before next dosing

Additional PK parameters may be calculated where appropriate.

Units for PK parameter output will be based on concentration units used in the study, unless otherwise specified. In case concentration data units change within the study, PK parameters will be reported using consistent units throughout study outputs.

The parameter C_{trough}, will be obtained directly from the concentration-time profiles

16.1.5 Presentation of PK Concentration and PK Parameter Data

16.1.5.1 Listings and Tables

The following PK tables will be produced (PK Analysis Set):

- Individual and descriptive statistics of concentrations by cohort, part, scheduled visit, and time window
- Individual and descriptive statistics of PK parameters by cohort, part, and scheduled visit
- Individual and descriptive statistics of dose normalized PK parameters by cohort, part, and scheduled visit

The following PK Listings will be produced (Safety Analysis Set):

- PK Sampling date, actual time, nominal time, deviation from time, percentage time deviation and concentration by participant analyte, matrix and group sorted in chronological order
- Concentration/PK parameter excluded from summaries/analyses

16.1.5.2 Graphical Summaries and Individual plots (PK Analysis Set)

- Day 1 and Day 15 individual concentration versus time plots; linear and semi-log; using the actual time points by participants, cohort, part, and scheduled visit; if any post-dose concentration is BLQ the line representing LLOQ may be added to the semi-log plots
- Day 1 and Day 15 overlaid individual concentration versus time plots; linear and semi-log; by cohort, part, and scheduled visit
- Day 1 and Day 15 arithmetic mean concentration time plots; linear (±SD for arithmetic mean) and semi-log; using scheduled (nominal) time points by cohort, part, and scheduled visit; if any post-dose concentration is BLQ the line representing LLOQ will be added to the semi-log plots
- Individual Ctrough values will be plotted against actual time points on a linear scale, for all participants by cohort and part.
- Mean Ctrough ±SD will be plotted by cohort and part, on a linear scale.

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17 References

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18 Appendices

18.1 Clinical Questionnaires

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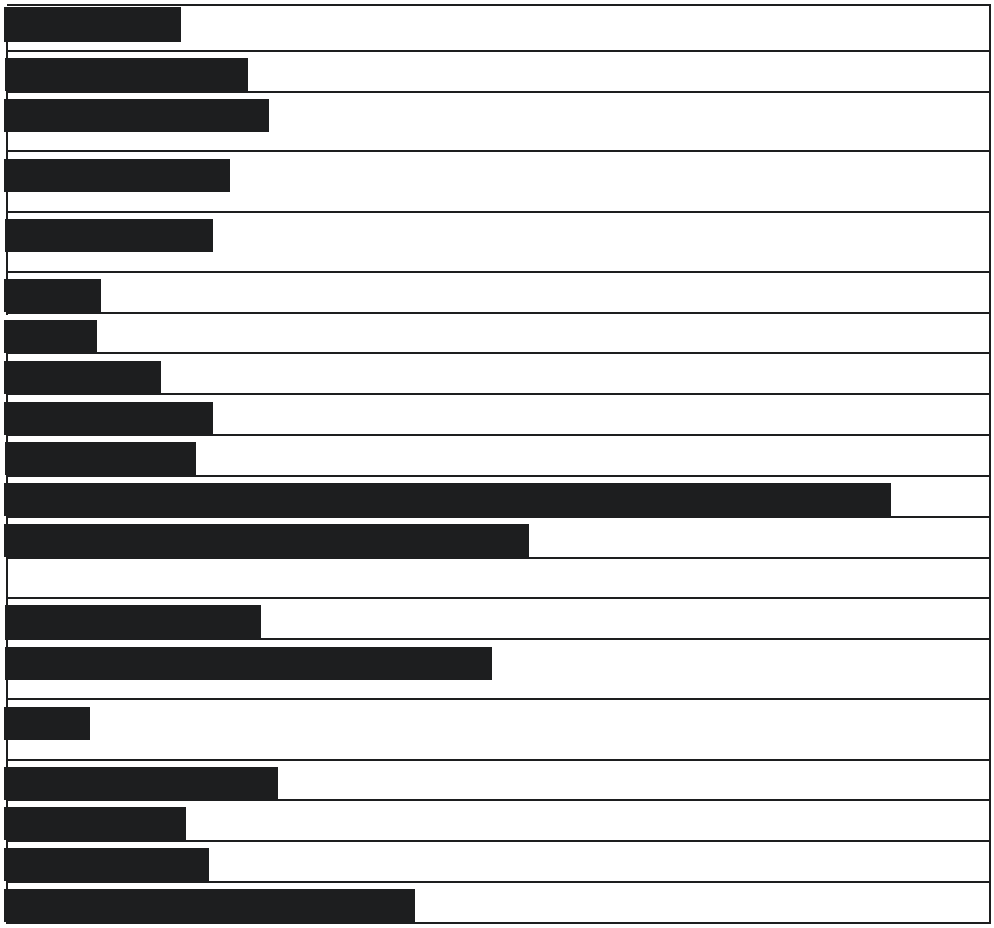

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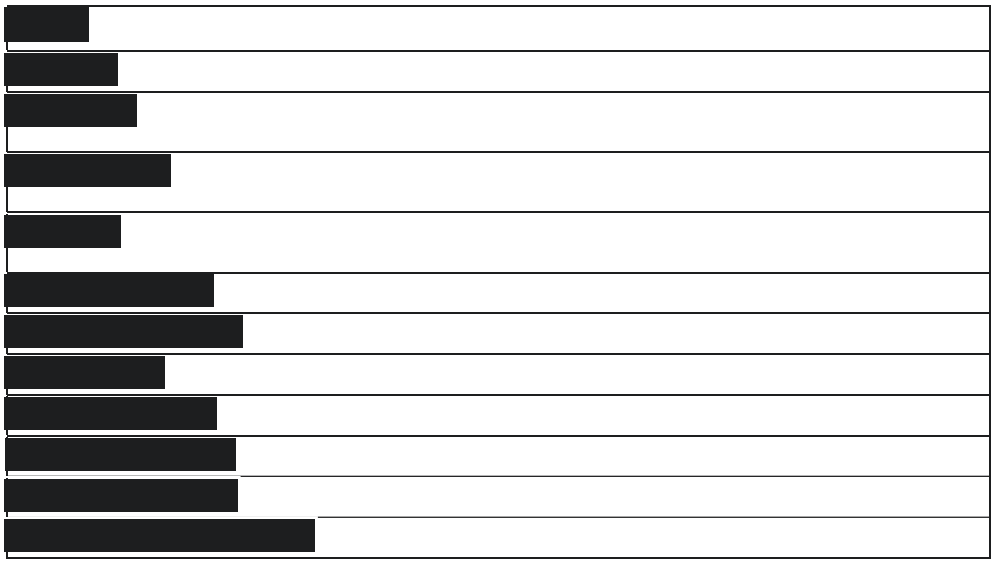

18.2 Corticosteroid Usage

18.2.1 General rules

To perform derivations with regards to CS use at Baseline or during the on-treatment period, the following rules will be applied:

- CS will be medications collected in the "CORTICOSTEROID MEDICATION DETAILS" eCRF form. CS collected in the "CONCOMITANT MEDICATIONS DETAILS" eCRF form will also be considered. Only CS for which indication is related to lupus (reason for medication = Disease related condition) will be considered.
- To derive topical CS use at Baseline, only CS medications with route = topical will be considered.
- To derive systemic CS use, only CS medications with route = oral, intravenous (including 'IV drip' and 'IV bolus'), intra-articular and intramuscular will be considered. Prednisone-equivalent CS dose will be derived for systemic use only.
- Concomitant CS medications are CS medications which are taken by participants any time during the on-treatment period, see section 9.8.
- When dose per administration or dosing frequency is missing or uninterpretable, the corresponding CS will not be included in CS dose derivation.

18.2.2 Missing dates handling

Start and end dates of CS medications will be imputed following the same rules as defined for the previous and concomitant medications (see Section 9.10).

18.2.3 Conversions

The tables below provide conversions to be performed in order to assess the CS dosage:

Table 6: Conversion factors in prednisone equivalent

Who-drug Term	Conversion factor in prednisone equivalent
METHYLPREDNISOLONE	1,25
METHYLPREDNISOLONE SODIUM / METHYLPREDNISOLONE SODIUM SUCCINATE	1.25
METHYLPREDNISOLONE ACETATE	1.25
HYDROCORTISONE / HYDROCORTISONE SODIUM SUCCINATE	0.25
BETAMETHASONE	6.667
BETAMETHASONE DIPROPIONATE	6.667
BETAMETHASONE VALERATE	6.667
BETAMETHASONE PHOSPHATE	6.667
DEXAMETHASONE	6.667
TRIAMCINOLONE / TRIAMCINOLONE ACETONIDE	1.25
CORTISONE	0.2
PREDNISOLONE	1
PREDNISONE	1
DEFLAZACORT	0.83333
MEPREDNISONE	1,25
PARAMETHASONE	2,5
CRONOLEVEL	6.667
BETROSPAM	6.667

Table 7: Frequency conversions for CS

Frequency	Conversion factor	Numerical Conversion factor
OAM	1/30	0.0333
QOD	1/2	0.5000
QW	1/7	0.1429
QWK	1/7	0.1429
BID/Q12	2	2.0000
TID/Q8	3	3.0000
QD – including QD with AM or PM (e.g. QD(AM), QD(PM), QD at AM, QD at PM)	1	1.0000
ONCE	1	1.0000
QAM	1	1.0000
Q2H	12	12.0000
Q3H	8	8.0000
Q4H	6	6.0000
Q6H	4	4.0000
Q8H	3	3.0000
Q12H	2	2.0000
Q24H	1	1.0000
QHS	1	1.0000
QID/Q6	4	4.0000
QPM	1	1.0000
QH	24	24.0000
Q3W	1/21	0.0476
Q3D	1/3	0.3333
TIW or Three times a week	3/7	0.4286
Four times a week	4/7	0.5714
Q4W, every 4 weeks	1/28	0.0357
BIW or Twice a week	2/7	0.2857
EVERY 3 HOURS	8	8.0000
X1	1	1.0000
EVERY OTHER DAY	1/2	0.5000
EVERY OTHER DAY ALTERNTATLY WITH30 MG Q0D	1/2	0.5000
EVERY OTHER DAY ALTERNTATLY WITH 20 MG QOD	1/2	0.5000
ONCE A WEEK, 1 TIME PER WEEK	1/7	0.1429
QD (EVERY MORNING)	1	1.0000
SINGLE DOSES	1	1.0000
ALTERNATE DAYS	1/2	0.5000
TWO TIMES A DAY	2	2.0000
4 DOSES GIVEN EVERY 2ND DAY	2	2.0000

18.2.4 Corticosteroid usage, daily dose

Prednisone-equivalent daily dose (mg) by visit (post-baseline visits):

- Prednisone-equivalent CS daily dose is equal to the total dose (mg) the participant is receiving at the date of the scheduled visit + 1 day (using conversion rules specified in section 18.2.3). If several CS are taken at the same scheduled visit, then all CS doses should be added.

CS dosing at Baseline is defined at CS dose taken the day of baseline visit (Day 1).


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