Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A Phase II, 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
Study Number:	MS200569_0003
Protocol Version:	28 September 2021/Version 1.0
Merck Compound:	M5049
Merck Registered Compound Name in Japan:	Not applicable
Study Phase:	Phase II
Short Title:	The WILLOW study with enpatoran in SLE and CLE (SCLE and/or DLE)
Acronym or Abbreviation:	WILLOW
Coordinating Investigator:	Eric Francis Morand, MBBS, PhD, FRACP Monash Health, 246 Clayton Rd, Clayton VIC 3168, Australia

Sponsor Name and Legal Registered Address:	Sponsor: Affiliates of Merck KGaA, Darmstadt, Germany For all countries, except the US and Canada: Merck Healthcare KGaA, Darmstadt, Germany an affiliate of Merck KGaA, Darmstadt, Germany Frankfurter Str. 250 64293, Darmstadt, Germany In the US and Canada: EMD Serono Research & Development Institute, Inc. an affiliate of Merck KGaA, Darmstadt, Germany 45A Middlesex Turnpike Billerica, MA, 01821, USA Local Sponsor for Sites in Japan: Merck Biopharma Co., Ltd. Japan an affiliate of Merck KGaA, Darmstadt, Germany Arco Tower, 1-8-1 Shimomeguro Meguro-ku, Tokyo 153-8926, Japan
Regulatory Agency Identifying Numbers:	IND: 145565 EudraCT: 2021-004648-27
Keywords	TLR7, TLR8, WILLOW, adults, SLE, CLE, lupus, discoid lupus erythematosus, subacute cutaneous lupus erythematosus, M5049, and enpatoran

Protocol Amendment Summary of Changes

Not applicable.

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	28 September 2021

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1 Protocol Summary

1.1 Synopsis

Protocol Title: A Phase II, Randomized, Double-Blind, Placebo-Controlled Dose-Ranging, Parallel and Adaptive Study to Evaluate the Efficacy and Safety of Enpatoran in Systemic Lupus Erythematosus (SLE) and in Cutaneous Lupus Erythematosus (CLE: Subacute Cutaneous Lupus Erythematosus [SCLE] and/or Discoid Lupus Erythematosus [DLE]) Participants Receiving Standard of Care

Short Title: The WILLOW study with enpatoran in SLE and CLE (SCLE and/or DLE)

Rationale: The purpose of this global Phase II, basket proof-of-concept (PoC) and dose-finding (DF) study is to evaluate the efficacy and safety of orally administered enpatoran over 24 weeks in participants with active SLE or CLE (active SCLE and/or DLE) in a randomized, double-blind, placebo-controlled, parallel, adaptive and dose-ranging setting.

M5049 (International nonproprietary name: enpatoran, hereafter used interchangeably in the protocol) is a small molecule, dual Toll-like receptor (TLR)7 and TLR8 antagonist shown to specifically inhibit the activation of TLR7/TLR8 by various ligands such as GU-rich single-stranded RNA sequences. Ligand activation of TLR7 and TLR8 stimulates antibody production, secretion of interferons (IFNs) and other cytokines, cellular maturation, and activation of other protective host mechanisms. Aberrant activation of TLR7 and TLR8 can result in an overreactive immune system and may act as a pathological mechanism driving progression of certain autoimmune diseases. The in vitro and in vivo properties of enpatoran suggest that this molecule may inhibit the pathological activity of RNA-containing immune complexes, and potentially resulting in reduced disease activity, decreased severity of lupus flares and reduced glucocorticoid requirements and in SLE and CLE patients.

Objectives and Estimands:

Objectives	Estimand attributes
Primary	
To evaluate the dose-response relationship of enpatoran in reducing disease activity based on Cutaneous Lupus Erythematosus Disease Area and Severity Index-A (CLASI-A)	Endpoint: Percent change from baseline in CLASI-A at Week 16
	Population: Patients with active SCLE, DLE or SLE with predominantly active lupus rash Note: Cohort A participants Treatment: Enpatoran vs placebo Intercurrent Event Strategy: - Early treatment discontinuation due to any reason: treatment policy - Protocol-prohibited medications, as determined by Endpoint Adjudication Committee (EAC): treatment policy - Corticosteroid use not compliant with protocol rules as determined by EAC: treatment policy Population-Level Summary: LS mean (SE) as estimated by Mixed model with repeated measures (MMRM). The Multiple Comparison Procedure – Modeling (MCP-Mod) procedure will be performed to evaluate the dose-response relationship.
To evaluate the dose-response relationship of enpatoran in reducing disease activity based on BILAG-Based Composite Lupus Assessment (BICLA) response rate	Endpoint: BICLA response at Week 24
	Population: Patients with active SLE Note: Cohort B participants Treatment: Enpatoran vs placebo Intercurrent Event Strategy: - Early treatment discontinuation due to any reason will be considered as non-responder (composite estimand strategy) - Protocol-prohibited medications, as determined by EAC will be considered as non-responder (composite estimand strategy) - Corticosteroid use not compliant with protocol rules as determined by EAC will be considered as non-responder (composite estimand strategy) Population-Level Summary: Responder rates and 95% CI. The MCP-Mod procedure will be performed to evaluate the dose-response relationship.
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)

Objectives	Estimand attributes
To evaluate the efficacy in disease control of enpatoran compared to placebo in lupus participants with active lupus rash	Endpoints: • Change from baseline in Cutaneous Lupus Activity Investigator's Global Assessment (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
	Population: Patients with active SCLE, DLE or SLE with active lupus rash Note: Active SCLE, DLE and SLE participants from Cohort A OR Cohort B with CLASI-A ≥ 8 at Screening and confirmed at Day 1 Intercurrent Event Strategy: - Early treatment discontinuation due to any reason: treatment policy - Protocol-prohibited medications, as determined by EAC: treatment policy - Corticosteroid use not compliant with protocol rules as determine by EAC: treatment policy 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: Patients with active SLE (Cohort B participants) Intercurrent Event Strategy: same as BICLA response Population-Level Summary: same as BICLA response.
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: Patients with active SCLE, DLE or SLE with predominantly active lupus rash Note: Active SCLE, DLE and SLE participants from Cohort A Intercurrent Event Strategy: same as BICLA response Population-Level Summary: number and proportion with 95% CI of participants achieving the respective response definition at Week 12 and Week 24.

Objectives	Estimand attributes
To evaluate the efficacy in disease control of enpatoran compared to placebo in participants with active SLE	Endpoint: • Systemic lupus erythematosus Responder Index-4 (SRI-4) response at Week 24 • Lupus Low Disease Activity State (LLDAS) attainment at Week 24 • Remission attainment at Week 24 • 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: Patients with active SLE Note: Cohort B participants Intercurrent Event Strategy: Same as BICLA response Population-Level Summary: Number and proportion with 95% CI of participants achieving the respective response definition at Week 12 and Week 24.
	Endpoints: • Change in the number of joints which are tender and swollen in 28-joint count from baseline at Week 24 • Change from baseline in Physician's Global Assessment at Week 24
	Population: as above Intercurrent Event Strategy: - Early treatment discontinuation due to any reason: treatment policy - Protocol-prohibited medications, as determined by EAC: treatment policy - Corticosteroid use not compliant with protocol rules as determine by EAC: treatment policy Population-Level Summary: Summary statistics at each visit
	Endpoints: • Time to first moderate/severe British Isles Lupus Assessment Group (BILAG) flare from Day 1 through Week 24 • Time to first SFI severe flare from Day 1 through Week 24
	Population: as above Intercurrent Event Strategy: - Early treatment discontinuation: treatment policy - Protocol-prohibited medications, as determined by EAC: composite strategy Population-Level Summary: HR and CI from stratified Cox model using randomization strata according to interactive voice/web response system (IVRS/IWRS), Kaplan-Meier estimates

Objectives	Estimand attributes
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 Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores at Week 24
	Population: Patients with active SCLE, DLE or SLE with active lupus rash. Note: Active SCLE, DLE and SLE participants from Cohort A OR Cohort B with CLASI-A ≥ 8 at Screening and confirmed at Day 1. Intercurrent Event Strategy: - Early treatment discontinuation due to any reason: treatment policy - Protocol-prohibited medications, as determined by EAC: treatment policy - Corticosteroid use not compliant with protocol rules as determine by EAC: treatment policy 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 Week 24
	Population: Patients with active SLE Note: Cohort B participants Intercurrent Event Strategy: - Early treatment discontinuation due to any reason: treatment policy - Protocol-prohibited medications, as determined by EAC: treatment policy - Corticosteroid use not compliant with protocol rules as determine by EAC: treatment policy Population-Level Summary: descriptive statistics at each visit and treatment difference at each study visit as estimated by MMRM.

Overall Design:

This is a global, Phase II, basket proof-of-concept and dose-finding, randomized, double-blind, placebo-controlled, dose-ranging, parallel and adaptive multicenter study in participants with active SLE or CLE (active SCLE and/or DLE) treated with standard of care to evaluate the efficacy and safety of enpatoran administered orally twice per day for 24 weeks.

Brief Summary:

- The purpose of this PoC and DF study is to evaluate the efficacy and safety of orally administered enpatoran over 24weeks in systemic lupus erythematosus (SLE) and cutaneous lupus erythematosus (CLE; subacute cutaneous lupus erythematosus [SCLE] and/or discoid lupus erythematosus [DLE]) patients in a randomized, double-blind, placebo-controlled, parallel, adaptive and dose-ranging setting.
- Study Duration: 33 weeks
- Visit Frequency: every 2 or 4 weeks
- Enpatoran is not available through an expanded access program.

Number of Participants: Up to 440 participants (100 in Cohort A + up to 340 in Cohort B) will be randomized, treated and followed-up in this study.

Study Intervention Groups and Duration:

The planned total duration of the study for each participant will be up to approximately 33 weeks: up to a 7-Week Screening Period (5-Week Screening Period with the possibility to expand by an additional 2 weeks if needed to repeat a laboratory test or due to an unanticipated event), a 24-Week Double-Blind Placebo-Controlled (DBPC) Treatment Period followed by a 2-Week Safety Follow-up Period. Upon completion of the eligibility form, and confirmation of eligibility of active SLE or CLE (active SCLE and/or DLE) by the Medical Monitor as well as Primary Investigator assessment that participant continues to meet inclusion/exclusion criteria, the participant will be randomized. The study will be conducted on an outpatient basis.

The study consists of 2 cohorts to establish PoC and dose-finding for enpatoran in 2 patient populations: Cohort B has a dose-finding adaptive design comprised of Part 1 and Part 2. Cohort A and Cohort B Part 1 will start in parallel with a subsequent initiation of Cohort B Part 2.

- Cohort A will have participants with CLE (active SCLE, and/or DLE) (CLASI-A $\geq$ 8) or SLE with predominantly active lupus rash (CLASI-A $\geq$ 8) and for SLE mild or no extra-mucocutaneous disease activity (BILAG 2004 1B, C, D [i.e., No BILAG 2004 A and No BILAG 2004 $\geq$ 2B]). Approximately 100 participants will be randomized 1:1:1:1 to enpatoran 25 mg twice per day (n=25): enpatoran 50 mg twice per day (n=25): enpatoran 100 mg twice per day (n=25): placebo twice per day (n=25).

- Cohort B will have SLE participants who have moderate to high systemic disease activity (BILAG $\geq$ 1A and/or 2B) with 1 or 2 of the following: CLASI-A $\geq$ 8 and/or SLEDAI $\geq$ 6. An adaptive design will be used for this cohort: Part 1 is designed to assess a clinical signal and based on an interim analysis of Part 1, Part 2 may be adapted to improve dose-finding in SLE, if needed.

    - Part 1 will be initiated first with approximately 60 participants randomized 1:2 to placebo vs enpatoran 100 mg twice per day to evaluate the futility of enpatoran vs placebo in SLE participants.

- Part 2 will be initiated after approximately 60 participants have been enrolled in Part 1 and participants will be randomized 1:1:1:1 to enpatoran 25 mg twice per day: enpatoran 50 mg twice per day: enpatoran 100 mg twice per day: placebo twice per day. An interim analysis is planned when the first 60 participants in Part 1 complete at least 12 weeks of treatment, or discontinue early, and will inform potential adaptations of dose and randomization ratio for Part 2 (maximum of 4 dose levels) if needed, or the decision to terminate Cohort B for futility. Participants from Cohort B will continue on their dose level initiated prior to any potential adaptation until completion of study treatment at Week 24 unless Cohort B is terminated for futility. Total sample size of Cohort B will not exceed 340 participants.

This study has interim analyses planned for Cohorts A and B.

Participants will self-administer study intervention twice per day at a set time each day unless a study visit day is planned. On scheduled study visit days, study intervention will be administered on-site after the scheduled pre-dose study assessment/procedures have been performed.

Protocol-specified corticosteroid tapering guidance and targets will be implemented in this study. Sites will be instructed to follow this guidance and must taper corticosteroids.

Participants who prematurely discontinue treatment are encouraged to remain in the study and follow the scheduled study visits after completion of the ET assessments as soon as possible. In case of study withdrawal, the ET Study Visit must occur as soon as possible and will replace the EOT Visit (and must subsequently be followed by Safety follow-up visits).

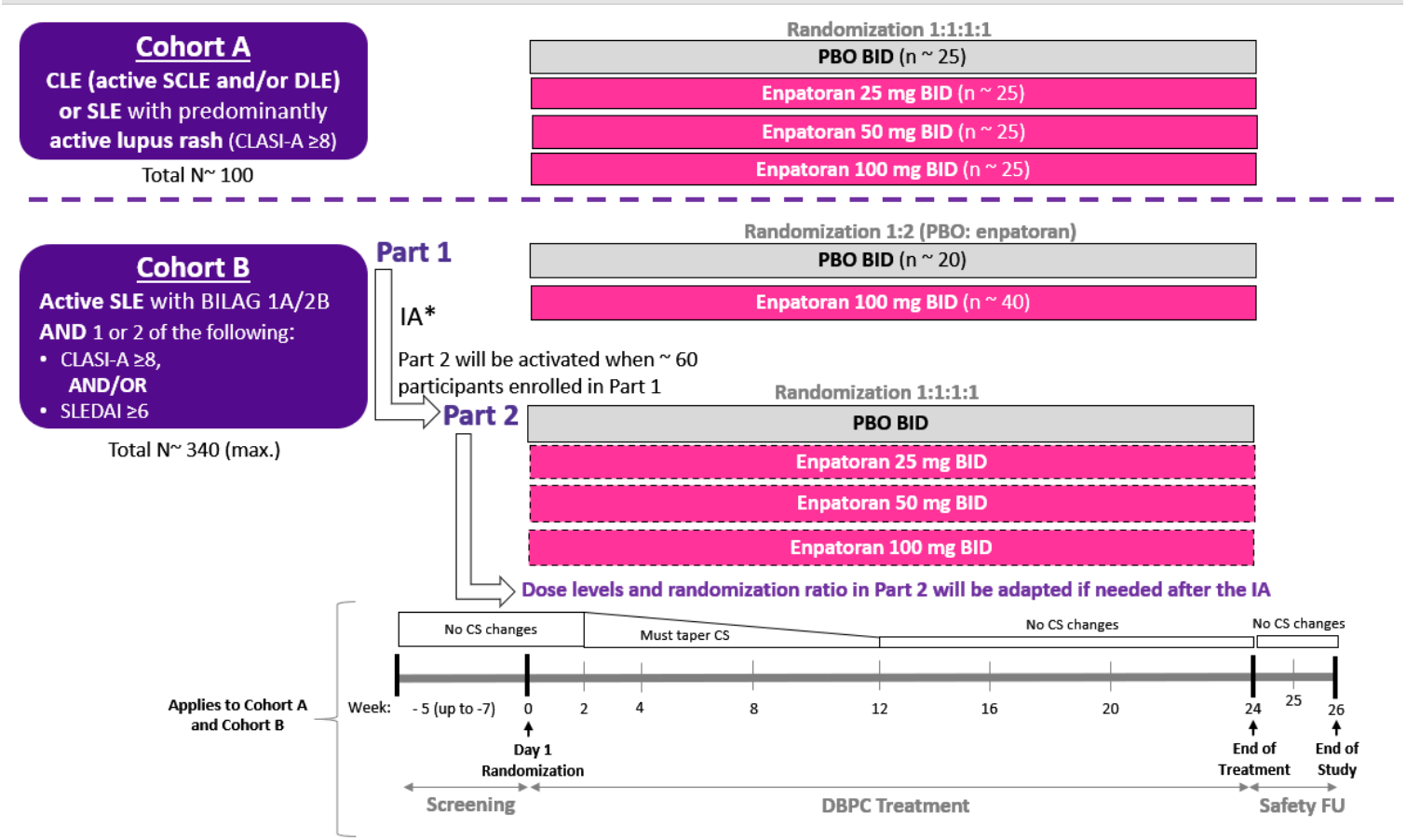
Participants who complete the 24-Week DBPC Treatment Period may be offered participation in an optional long-term extension (LTE) study as part of a separate protocol.

Involvement of Special Committees: Yes

Special oversight committees will include External Independent Data Monitoring Committee, Study Steering Committee, Endpoint Adjudication Committee, and Firewall team. The Firewall team will be composed of a restricted group of individuals within the Sponsor team who are not directly involved in the study conduct activities.

1.2 Schema

Figure 1 Study Schema



Cohort A and Cohort B Part 1 will start in parallel with subsequent initiation of Cohort B Part 2.

*Interim analyses when ~ 60 participants enrolled in Cohort B Part 1 have completed at least 12 weeks of treatment (see Sequence of Analyses for details and other analyses).

Participants who complete the 24-Week DBPC Treatment Period may be offered participation in an optional long-term extension (LTE) study as part of a separate protocol.

BID=twice per day; BILAG=British Isles Lupus Assessment Group; CLASI=Cutaneous Lupus Erythematosus Disease Area and Activity Index; CLE=Cutaneous Lupus Erythematosus; CS=Corticosteroids; DLE=Discoid Lupus Erythematosus; DBPC=Double-Blind Placebo-Controlled; FU=Follow-up; IA=interim analysis; PBO=placebo; SLE=Systemic Lupus Erythematosus; SLEDAI=Systemic Lupus Erythematosus Disease Activity Index; SCLE=Subacute Cutaneous Lupus Erythematosus.

1.3 Schedule of Activities

Table 1 Schedule of Assessments

		DBPC Treatment Period									Safety Follow-up[c]		Notes
Assessments and Procedures (Weeks)	**Screening –7 to -5**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ EOT[a]**	**ET[b]**	**25** ☎	**26**	5-Week Screening Period with the possibility to expand by an additional 2 weeks if needed to repeat a laboratory test or due to an unanticipated event, upon Medical Monitor approval. Minimum Screening period is 2 weeks.
Study Day	**-49 to -1**	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**-**	**176**	**183**	
Visit Window (Days)			**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**+ 3**	**+ 3**	**+ 3**	
Informed consent	X												
Pharmacogenetic consent	X												Optional (can be collected at any timepoint during the study before sample collection).
Inclusion/ exclusion criteria	X	X*											*Recheck clinical status, clinical hybrid SELENA-SLEDAI (without laboratory parameters) and CLASI-A score for relevant participant prior to randomization. See Section 5.1 and Section 5.2.
Eligibility Packet	X												Submission as soon as possible after the Screening Visit.
Demographics	X												See Section 5.
Past and current medical conditions, medications	X												Within 12 months prior to the Screening visit, history or current alcohol, substance, or drug abuse, relevant medication including medication history for the treatment of SLE and CLE and flare history.

		DBPC Treatment Period									Safety Follow-up[c]		Notes
Assessments and Procedures (Weeks)	**Screening -7 to -5**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ EOT[a]**	**ET[b]**	**25** ☎	**26**	5-Week Screening Period with the possibility to expand by an additional 2 weeks if needed to repeat a laboratory test or due to an unanticipated event, upon Medical Monitor approval. Minimum Screening period is 2 weeks.
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Visit Window (Days)			**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**+ 3**	**+ 3**	**+ 3**	
SCLE or DLE diagnosis: Historical pathology report for skin biopsy OR Fresh skin biopsy	X												Participants with cutaneous lupus lesions unsuitable for biopsy (e.g., malar rash, bridge of the nose, scalp) will be evaluated by skin photography instead. See Inclusion criterion 3, Section 5.1.
Documentation of SLE, SCLE and/or DLE classification criteria	X												See Section 5.1.
Chest imaging	X												See Exclusion criterion 32, Section 5.2.
SARS-CoV-2 test	X												Only if required. See Section 5.2.
Serum pregnancy test	X												WOCBP only (see Section 5.1).
Serum virology (Hepatitis B and C screening, HIV)	X												See Section 5.2.
TB assessment	X												See Section 5.2.
TSH	X												See Section 5.2.
FSH and estradiol	X												Women of nonchildbearing potential only to determine postmenopausal status. See Section 8.2.4.
ANA	X												See Inclusion criterion 8, Section 5.1.
IFN-GS	X												**SLE participants only.** See Section 8.6.

		DBPC Treatment Period									Safety Follow-up[c]		Notes
Assessments and Procedures (Weeks)	**Screening -7 to -5**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ EOT[a]**	**ET[b]**	**25 ☎**	**26**	5-Week Screening Period with the possibility to expand by an additional 2 weeks if needed to repeat a laboratory test or due to an unanticipated event, upon Medical Monitor approval. Minimum Screening period is 2 weeks.
Study Day	**-49 to -1**	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**-**	**176**	**183**	
Visit Window (Days)			**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**+ 3**	**+ 3**	**+ 3**	
SARS-CoV-2 symptoms or close contact	X												Within 3 to 5 days prior to randomization, to determine if SARS-CoV-2 testing (accepted according to local guidelines) should be performed (or repeated). See Section 5.2.
Randomization and Study Intervention													
Randomization		X											Participant eligibility to the appropriate cohort to be confirmed on Day 1 prior to randomization. See Section 5.
Study intervention		←----------											Twice per day administration with one glass of water (200 mL) and no food restrictions. On scheduled study visit days, the participant will be asked not to self-administer study intervention at home and hold the dose until pre-dose assessments have been completed in the clinic. Last study intervention administration will be prior to the EOT visit for those who opt out for the separate LTE study. See Section 6.

		DBPC Treatment Period									Safety Follow-up[c]		Notes
Assessments and Procedures (Weeks)	**Screening -7 to -5**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ EOT[a]**	**ET[b]**	**25** ☎	**26**	5-Week Screening Period with the possibility to expand by an additional 2 weeks if needed to repeat a laboratory test or due to an unanticipated event, upon Medical Monitor approval. Minimum Screening period is 2 weeks.
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Visit Window (Days)			**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**+ 3**	**+ 3**	**+ 3**	
Exposure data documentation		←----------											Participants to record date, time, and amount of study intervention administration in the paper diary card or mobile application provided. See Section 6.2.
Mealtime documentation		←----------											On scheduled study visit days with PK assessment, record the date and time of the closest meal before and after the study drug administration. See Section 5.3.1.
Study intervention accountability		X	X	X	X	X	X	X	X	X			See Section 6.2.
Patient Reported Outcome Questionnaires and Assessments (See Appendix 8). PROs will be administered in electronic format. PRO assessments will be completed prior to administration of study intervention and prior to any other study assessment(s), wherever possible.													
FACIT-Fatigue		X		X	X	X			X	X		X	**All participants**
MOS Sleep Scale		X		X		X			X	X		X	**All participants**
Patient experience in-trial interviews									X	X			Selected sites. Within 2 weeks of the EOT/ET visit.
SLE symptoms (Lupus SSD)		X		X	X	X			X	X		X	**SLE in Cohort B only.**
PROMIS Physical Function 10a		X		X		X			X	X		X	**SLE in Cohort B only.**

		DBPC Treatment Period									Safety Follow-up[c]		Notes
Assessments and Procedures (Weeks)	**Screening -7 to -5**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ EOT[a]**	**ET[b]**	**25 ☎**	**26**	5-Week Screening Period with the possibility to expand by an additional 2 weeks if needed to repeat a laboratory test or due to an unanticipated event, upon Medical Monitor approval. Minimum Screening period is 2 weeks.
Study Day	**-49 to -1**	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**-**	**176**	**183**	
Visit Window (Days)			**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**+ 3**	**+ 3**	**+ 3**	
PtGA		X		X	X	X			X	X		X	**SLE in Cohort B only.**
PGIC				X	X	X			X	X		X	**SLE in Cohort B only.**
Skin PtGA		X	X	X	X	X			X	X		X	**SCLE, DLE & SLE with active skin rash (CLASI-A ≥8 at Screening and Day 1 in Cohort A or B).**
Skin PGIC			X	X	X	X			X	X		X	**SCLE, DLE & SLE with active skin rash (CLASI-A ≥8 at Screening and Day 1 in Cohort A or B).**
Skindex 29+3		X		X	X	X			X	X		X	**SCLE, DLE & SLE with active skin rash (CLASI-A ≥8 at Screening and Day 1 in Cohort A or B).**
Itch NRS		X	X	X	X	X			X	X		X	**SCLE, DLE & SLE with active skin rash (CLASI-A ≥8 at Screening and Day 1 in Cohort A or B).**
Clinical Assessments													
Adverse event review	←----------											→----------	Continuous throughout study. See Section 8.3.
Concomitant therapy review		X	X	X	X	X	X	X	X	X	X	X	

		DBPC Treatment Period									Safety Follow-up[c]		Notes
Assessments and Procedures (Weeks)	**Screening –7 to -5**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ EOT[a]**	**ET[b]**	**25 ☎**	**26**	5-Week Screening Period with the possibility to expand by an additional 2 weeks if needed to repeat a laboratory test or due to an unanticipated event, upon Medical Monitor approval. Minimum Screening period is 2 weeks.
Study Day	**-49 to -1**	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**-**	**176**	**183**	
Visit Window (Days)			**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**+ 3**	**+ 3**	**+ 3**	
Physical examination including routine neurological examination	X	X	X	X	X	X	X	X	X	X		X	See Section 8.2.1.
Vital signs	X	X	X	X	X	X	X	X	X	X		X	Height collected at Screening visit only. BMI calculated at Screening only. Obtain vital signs before any scheduled ECG. See Section 8.2.2.
ECG	X	X			X			X	X	X			Day 1: predose (as Baseline) and 1-2 hour postdose. All other days except for Day 1: 1-2 hour postdose. Corrected using Fridericia's formula. See Section 8.2.3.
C-SSRS	X	X		X	X	X	X	X	X	X		X	See Appendix 8.
CLASI	X	X*	X	X	X	X	X	X	X	X		X	**All participants (Cohort A or B)** *Re-check for relevant participant prior to randomization. See Appendix 8.
Skin photography	X*	X	X	X	X		X		X	X			*Screening visit: required to confirm SCLE and/or DLE diagnosis for Cohort A participants with only historical skin biopsy and for participants with skin lesions unsuitable for biopsy (e.g., malar rash, bridge of the nose, scalp). Optional for participants with fresh skin biopsy. All other days: optional for Cohort A participants at selected sites only. See Section 8.1.

		DBPC Treatment Period									Safety Follow-up[c]		Notes
Assessments and Procedures (Weeks)	**Screening -7 to -5**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ EOT[a]**	**ET[b]**	**25 ☎**	**26**	5-Week Screening Period with the possibility to expand by an additional 2 weeks if needed to repeat a laboratory test or due to an unanticipated event, upon Medical Monitor approval. Minimum Screening period is 2 weeks.
Study Day	**-49 to -1**	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**-**	**176**	**183**	
Visit Window (Days)			**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**+ 3**	**+ 3**	**+ 3**	
CLA-IGA	X	X	X	X	X	X	X	X	X	X		X	**SCLE, DLE & SLE with active skin rash (CLASI-A ≥ 8 at Screening and Day 1 in Cohort A or B).** See Appendix 8.
Physician's Global Assessment of Cutaneous Lupus Disease Activity	X	X	X	X	X	X	X	X	X	X		X	**SCLE, DLE & SLE with active skin rash (CLASI-A ≥ 8 at Screening and Day 1 in Cohort A or B).** See Appendix 8.
Hybrid SELENA-SLEDAI	X	X*		X	X	X	X	X	X	X		X	**All SLE participants (Cohort A or B).** *Re-check clinical hybrid SELENA-SLEDAI (without laboratory parameters) for relevant participant prior to randomization. See Appendix 8.
Physician's Global Assessment of SLE Disease Activity	X	X		X	X	X	X	X	X	X		X	**All SLE participants (Cohort A or B).** See Appendix 8.
28-joint count	X	X		X	X	X	X	X	X	X		X	**Screening: SLE participants.** **Day 1 and subsequent visits: SLE participants in Cohort B only.** See Appendix 8.
BILAG 2004	X	X		X	X	X	X	X	X	X		X	Screening visit: BILAG 2004 will be assessed for all SLE participants to determine Cohort A or B assignment. **Day 1 and subsequent visits: SLE participants in Cohort B only.** See Appendix 8.

		DBPC Treatment Period									Safety Follow-up[c]		Notes
Assessments and Procedures (Weeks)	**Screening -7 to -5**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ EOT[a]**	**ET[b]**	**25** ☎	**26**	5-Week Screening Period with the possibility to expand by an additional 2 weeks if needed to repeat a laboratory test or due to an unanticipated event, upon Medical Monitor approval. Minimum Screening period is 2 weeks.
Study Day	**-49 to -1**	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**-**	**176**	**183**	
Visit Window (Days)			**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**+ 3**	**+ 3**	**+ 3**	
BILAG-2004 associated laboratory tests (anticardiolipin, lupus anticoagulant, haptoglobin, and Coombs)	X	X		X	X	X	X	X	X	X		X	The anticardiolipin, lupus anticoagulant, and haptoglobin blood specimens will be collected at all specified visits, however the blood will be stored at the central laboratory and the analyses performed only if the Investigator indicates that these tests need to be completed because of clinical suspicion of hemolytic anemia or antiphospholipid syndrome. Direct Coombs test samples will only be collected per the Investigator's opinion and applicable BILAG assessment requirements for determining hemolytic anemia. Screening visit: BILAG 2004 will be assessed in all SLE participants to determine Cohort A or B assignment. **Day 1 and subsequent visits: SLE participants in Cohort B only.**
SFI	X	X		X	X	X	X	X	X	X		X	**Screening: SLE participants.** **Day 1 and subsequent visits: SLE participants in Cohort B only.** See Appendix 8.
MoCA		X							X	X			**SLE in Cohort B only.** See Appendix 8.

		DBPC Treatment Period									Safety Follow-up[c]		Notes
Assessments and Procedures (Weeks)	**Screening -7 to -5**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ EOT[a]**	**ET[b]**	**25** ☎	**26**	5-Week Screening Period with the possibility to expand by an additional 2 weeks if needed to repeat a laboratory test or due to an unanticipated event, upon Medical Monitor approval. Minimum Screening period is 2 weeks.
Study Day	**-49 to -1**	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**-**	**176**	**183**	
Visit Window (Days)			**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**+ 3**	**+ 3**	**+ 3**	
Clinical Safety Laboratory Assessments													
UPCR	X	X		X	X	X	X	X	X	X		X	Before morning of collection, provide participant with specimen cup. The participant will collect first morning void, clean-catch midstream sample at home in the morning of clinic visit and bring to the site. See Appendix 5.
Urinalysis (urine dipstick and microscopy)	X	X		X	X	X	X	X	X	X		X	The same sample taken for UPCR may be used to perform the urinalysis. See Appendix 5.
Total Testosterone, LH, FSH		X				X			X	X		X	For male participants. Preferably morning samples. See Appendix 5.
Urine pregnancy test		X	X	X	X	X	X	X	X	X			WOCBP only. Checked before enrollment/randomization and each clinic visit. Local laboratory test. See Appendix 5.
Routine hematology, chemistry	X	X	X	X	X	X	X	X	X	X		X	See Appendix 5.
Amylase, lipase	X	X											Additional tests may be assessed as clinically indicated (per Investigator's judgment). See Appendix 5.

		DBPC Treatment Period									Safety Follow-up[c]		Notes
Assessments and Procedures (Weeks)	**Screening -7 to -5**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ EOT[a]**	**ET[b]**	**25** ☎	**26**	5-Week Screening Period with the possibility to expand by an additional 2 weeks if needed to repeat a laboratory test or due to an unanticipated event, upon Medical Monitor approval. Minimum Screening period is 2 weeks.
Study Day	**-49 to -1**	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**-**	**176**	**183**	
Visit Window (Days)			**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**+ 3**	**+ 3**	**+ 3**	
Vaccine immunization status		X							X				Antibody titers to tetanus toxoid, diphtheria toxoid, pneumococcal and SARS-CoV-2 antigens. See Appendix 5.
Pharmacokinetic and Pharmacodynamic Assessments													
Predose PK		X	X	X	X	X							PK blood collection must be done within 60 minutes prior to the morning dose administration. Hold the morning dose of study intervention, which will be administered after predose PK blood collection. See Section 8.4.
Postdose PK		X	X		X		X	X	X				Day 1 and Week 2: Blood collected between 1-2 hours post-dose and between 4-6 hours post-dose (last assessment before the study participant leaves). Week 8: Blood collected between 1-2 hours post-dose. Week 16, Week 20, and Week 24: Blood collected any time of the visit. Record PK sampling time. See Section 8.4.
Serum biomarkers		X	X	X		X	X		X	X		X	Including but not limited to cytokines. See Section 8.6
Immunoglobulins	X*	X				X			X	X		X	IgG, IgA, IgM; Screening visit: *IgG only. See Section 8.6.

		DBPC Treatment Period									Safety Follow-up[c]		Notes
Assessments and Procedures (Weeks)	**Screening -7 to -5**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ EOT[a]**	**ET[b]**	**25** ☎	**26**	5-Week Screening Period with the possibility to expand by an additional 2 weeks if needed to repeat a laboratory test or due to an unanticipated event, upon Medical Monitor approval. Minimum Screening period is 2 weeks.
Study Day	**-49 to -1**	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**-**	**176**	**183**	
Visit Window (Days)			**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**+ 3**	**+ 3**	**+ 3**	
Gene expression (RNA)		X	X	X		X	X		X	X		X	Day 1: Predose sample - hold the morning dose of study intervention, which will be administered after predose blood collection. All other days: Blood collected any time of the visit. See Section 8.6.
Pharmacogenetics (DNA)		X											Optional (can be collected at any timepoint during the study post consent). See Section 8.5.
Immune cell subsets		X		X		X			X	X		X	Collect predose, if possible. Only in selected sites. See Section 8.6.
Skin biopsy		X		X									Highly encouraged (optional). Biopsy active lupus skin lesion preferably from the same target lesion at baseline and Week 4. See Section 8.6.
SLE disease activity markers	X	X		X	X	X	X	X	X	X		X	Anti-dsDNA antibodies; Complement C3, C4, CH50. **All SLE participants (Cohort A or B).** See Section 8.6.
Anti-ENA Abs	X*	X							X	X			anti-Sm, -RNP, -Ro/SSA, and -La/SSB Abs. See Section 8.6. ***Screening visit: all SLE participants.** **Day 1 and subsequent visits: all study participants in Cohort A or B (CLE or SLE).**

		DBPC Treatment Period									Safety Follow-up[c]		Notes
Assessments and Procedures (Weeks)	**Screening -7 to -5**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24/ EOT[a]**	**ET[b]**	**25** ☎	**26**	5-Week Screening Period with the possibility to expand by an additional 2 weeks if needed to repeat a laboratory test or due to an unanticipated event, upon Medical Monitor approval. Minimum Screening period is 2 weeks.
Study Day	**-49 to -1**	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**-**	**176**	**183**	
Visit Window (Days)			**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**+ 3**	**+ 3**	**+ 3**	
Antiphospholipid Abs		X							X				Anti-cardiolipin IgG, IgM; anti-β2 glycoprotein IgG, IgM; Lupus anticoagulant (dRVVT or other) **SLE in Cohort B only.** See Section 8.6.

a The DBPC Week 24/EOT Visit (Table 1) may be the LTE Day 1 Visit (offered under a separate protocol). If a participant rolls over to the LTE, complete only the assessments for the LTE Day 1 Visit, not the DBPC Week 24/EOT Visit.

b Participants who discontinue treatment early are encouraged to remain in the study and should complete the ET assessments as soon as possible and revert to the same study schedule (Table 1) based on the participant's Day 1 visit until the Safety follow-up visits are completed. In case of study withdrawal, the ET Study Visit must occur as soon as possible and will replace the EOT Visit (and must subsequently be followed by the Safety follow-up visits).

c Safety follow-up visits are not required for participants who enroll in the LTE study (as part of a separate protocol) at the Week 24 Visit.

ANA = antinuclear antibody, anti-Sm= anti-Smith, anti-RNP = antinuclear ribonucleoprotein, BILAG = British Isles Lupus Assessment Group, BMI = Body mass index, CLA-IGA = Cutaneous Lupus Activity Investigator's Global Assessment, CLASI = Cutaneous Lupus Erythematosus Disease Area and Activity Index, CLE = cutaneous lupus erythematosus, C-SSRS = Columbia-Suicide Severity Rating Scale, DBPC= Double-Blind Placebo-Controlled, DLE= Discoid lupus erythematosus, dsDNA = double-stranded DNA, dRVVT = Dilute Russell Viper Venom Time, ECG = electrocardiogram, EOT = End of Treatment, ET = Early Termination, ENA = Extractable Nuclear Antigen Antibodies, FACIT = Functional Assessment of Chronic Illness Therapy, FSH = Follicle-stimulating hormone, HIV = human immunodeficiency virus, IFN-GS = Type I-interferon gene signature, Ig = immunoglobulin, LH = Luteinizing hormone, LTE = Long-term extension, MoCA= Montreal Cognitive Assessment, MOS = Medical Outcomes Study Sleep Scale, NRS = Numeric Rating Scale, PtGA= Patient Global Assessment, PGIC = Patient Global Impression of Change, PK = pharmacokinetic(s), PROMIS = Patient-Reported Outcomes Measurement Information System, SARS-CoV-2 = Severe acute respiratory syndrome coronavirus-2, SCLE = Subacute Cutaneous Lupus Erythematosus, SELENA= Safety of Estrogens in Systemic Lupus Erythematosus National Assessment, SLEDAI = Systemic Lupus Erythematosus Disease Activity Index, SFI= SELENA-SLEDAI Flare Index, SLE = Systemic Lupus Erythematosus, SSD= Symptom Severity Diary, TB = tuberculosis, TSH = thyroid stimulating hormone, UPCR= Urine protein/creatinine ratio, WOCBP = women of childbearing potential.

2 Introduction

M5049 (International nonproprietary name: enpatoran, hereafter used interchangeably in the protocol) is a small molecule, dual Toll-like receptor 7 and 8 (TLR7 and TLR8) antagonist shown to specifically inhibit the activation of TLR7/8. The in vitro and in vivo properties of enpatoran suggest that this molecule has a potential to inhibit TLR7/8-associated pathology and to decrease disease flares and progression in participants suffering from systemic lupus erythematosus (SLE) and cutaneous lupus erythematosus (active subacute cutaneous lupus erythematosus [SCLE] and/or discoid lupus erythematosus [DLE]).

Detailed information on the chemistry, pharmacology, efficacy, and safety of enpatoran is in the Investigator's Brochure (IB).

2.1 Study Rationale

The purpose of this global Phase II, basket proof-of-concept (PoC) and dose-finding study is to evaluate the efficacy and safety of orally administered enpatoran in active SLE and CLE (active SCLE and/or DLE) patients in a randomized, double-blind, placebo-controlled, parallel, adaptive and dose-ranging 24-Week study. The study design and participant safety surveillance are based on enpatoran data obtained from the first-in-human (FIH) Phase I single and multiple ascending dose healthy volunteer pharmacokinetic (PK) study (NCT0367632), the ongoing SLE and CLE Phase I multiple ascending dose study (NCT04647708) and COVID-19 pneumonia Phase II study (NCT04448756), nonclinical evaluation of enpatoran, and results from clinical studies of other interferon (IFN) suppressive agents in active SLE and CLE (active SCLE and/or DLE).

Cutaneous lupus erythematosus (CLE: active SCLE and/or DLE) and SLE are in the same spectrum of lupus erythematosus that share some common disease characteristics (mucocutaneous manifestations) and pathogenesis (e.g., apoptosis, inefficient clearance of cell debris, TLR7/8 activation, excessive type I IFN production) while differing mainly in the extent of organ involvement - mucocutaneous involvement in CLE (active SCLE and/or DLE) compared with multi-organ systemic involvement in SLE.

Enpatoran is a small molecule, dual TLR7 and TLR8 antagonist shown to specifically inhibit the activation of TLR7/TLR8 by various ligands such as GU-rich single-stranded RNA sequences. Ligand activation of TLR7 and TLR8 stimulates antibody production, secretion of interferons (IFNs) and other cytokines, cellular maturation, and activation of other protective host mechanisms. Aberrant activation of TLR7 and TLR8 can result in an overreactive immune system and may act as a pathological mechanism driving progression of certain autoimmune diseases. The in vitro and in vivo properties of enpatoran suggest that this molecule may inhibit the pathological activity of RNA-containing immune complexes, and potentially resulting in reduced disease activity, decreased severity of lupus flares and reduced glucocorticoid requirements and in SLE and CLE patients.

2.2 Background

Systemic lupus erythematosus is an autoimmune disease that can affect multiple organ systems and can be unpredictable in disease severity, with active disease which in some cases manifests as flares alternating with periods of lower activity. Skin involvement occurs in 70% to 80% of all patients with lupus erythematosus (Zeidi 2019). Disease prevalence is approximately 1 in 1000 individuals overall but varies with gender and ethnicity and is higher in women (female:male ratio = 9:1) and African American or other non-Caucasian populations. The cutaneous manifestations of lupus erythematosus (both SLE and CLE) include a broad spectrum of clinical and histopathological findings, on which classification is based. Multi-organ involvement distinguishes SLE from CLE, but detailed biomarker studies demonstrate the two have many overlapping features, including elevated Type I-interferon gene signature (IFN-GS) expression (Braunstein 2012). Around 17% of CLE patients progress to SLE based on the American College of Rheumatology (ACR) criteria, fulfilled mostly on the mucocutaneous criteria (Kuhn 2014).

Cutaneous lupus erythematosus is categorized into acute, subacute, chronic, and intermittent based on clinical history and morphological characteristics that were initially established by Gillian (Kuhn 2014); in Europe the more specific European Society of Cutaneous Lupus Erythematosus criteria (Sigges 2013) were established to further categorize CLE patients for reasons of prognosis and treatment. Overall, the most common forms of CLE in patients who do not have SLE are subacute cutaneous lupus erythematosus (SCLE; annular and papulosquamous) and discoid lupus erythematosus (DLE) (Ziemer 2014).

Corticosteroids (CS; including topical) remain a therapeutic mainstay for short- and long-term control of disease activity in both SLE and CLE and are often administered in combination with chloroquine derivatives (Petri 2006). However, approximately one-third of CLE patients never respond to antimalarials (Chang 2011). Both SLE and CLE patients are chronically exposed to CS and other medication, including general immunosuppressive agents, with significant side effects (Fauci 2008; Jimenez 2003; Moghadam-Kia 2009). Topical calcineurin inhibitors are also used in CLE. However, the options for more aggressive treatment regimens for both SLE and CLE remain limited despite the treatment advances for other autoimmune diseases; the toxicity of the more aggressive drug regimens for SLE contribute significantly to morbidity and mortality. Also, there are no approved therapies for CLE, although when required, the off-label systemic treatments commonly used are mostly the same as those for SLE (Ziemer 2014).

Genome-wide association studies, experimental mouse models, and translational studies have provided evidence for the involvement of TLR7 and TLR8 in SLE and CLE pathogenesis. Production of antinuclear antibodies (ANA), including anti-ssRNA antibodies (e.g., anti-Sm, Ro/SSA, La/SSB, RNP) are frequently observed in SLE and CLE patients (Wenzel 2019, Wu 2015). These antibodies can form RNA-containing immune complexes that can activate intracellular signaling pathways via TLR7 and TLR8. Activation results in Type I IFN and inflammatory cytokine (e.g., IL-6, TNFα) release from various immune cells and cells with immune function leading to local and systemic inflammation and organ damage. Type I IFN release and IFNα/β receptor signaling leads to transcription of interferon-induced genes that can be measured as elevated Type I interferon-gene signature (IFN-GS) expression. Type I IFN gene

signature is increased in SCLE and DLE and correlates with cutaneous disease activity (Braunstein 2012) and skin biopsies from people with either CLE or SLE demonstrate significantly increased expression of Type I IFN-GS (Lehman 2019). Reports from clinical studies indicate that pDC depletion and suppression of Type I IFNs lead to a substantial reduction in SLE and CLE disease activity (Furie 2019, Morand 2020, Furie 2020; Werth 2020). Conversely, treatment with IFNα or topical TLR7 agonists induces reversible lupus-like symptoms (Burnett 2010, Lee 2010, Niewold 2005, Yokogawa 2014).

The in vivo efficacy of M5049 was evaluated in mouse models of SLE; daily oral administration showed strong efficacy in preventing disease development in both models studied. M5049 showed improved survival and reduction in proteinuria and disease biomarkers (i.e., autoantibody levels and IFN-GS expression) in the BXSB Y-linked autoimmune acceleration (Yaa) model and prevented the development of kidney damage and reduced proteinuria and autoantibody levels in an IFN accelerated NZB/W F1 model.

In the FIH study (NCT03676322), M5049 administered as single-dose or repeat doses up to 200 mg daily in healthy participants suppressed secretion of ex vivo-stimulated cytokines including IL-6, TNFα, and IFNα in an exposure-dependent manner.

Additional information on the pharmacology, pharmacodynamics (PD), and safety of M5049 is provided in the IB.

2.3 Benefit/Risk Assessment

There is a high unmet medical need for novel therapies with an improved benefit/risk ratio to decrease the disease manifestations of SLE/CLE and increase the affected person's overall quality of life (Fanouriakis 2019, Lauren 2013). More specifically, novel therapies should be effective in controlling the cutaneous, articular, renal, and nervous system manifestations of the disease. New therapeutic agents for SLE need to reduce the dependence on CS and toxic immunosuppressive agents, while also controlling end-organ damage, reducing morbidity, and mortality and improving the quality of life. In addition, there are no therapies approved for the treatment of CLE, and generally systemically toxic medications that control SLE flares are used off-label for CLE. A therapy for controlling subacute cutaneous or discoid lupus would dramatically improve those patients' quality of life.

Due to the heterogenous nature of the disease, a wide spectrum of therapies is being used depending on the organ involvement, severity, and comorbidities. These therapeutic options include antimalarials (hydroxychloroquine, chloroquine), corticosteroids [CS], immunosuppressant agents (e.g. azathioprine [AZA], mycophenolate mofetil [MMF], and cyclophosphamide [CYC]) and biologics (e.g. rituximab and belimumab). In addition, other disease modifying antirheumatic drugs (DMARDs) such as methotrexate [MTX], leflunomide, and calcineurin inhibitor are also being used. The available product data show that infections, neuropsychiatric toxicity (seizures, tremors, headache, dizziness, anxiety, nervousness suicidal behavior and ideation & psychotic disorder), cardiac disorder including ventricular arrythmias and prolonged QT interval have been experienced at variable frequency (very common to rare) by some patients on these therapies. Moreover, most of these drugs are associated with embryofetal development toxicity. Drug-induced effects on human fertility have not been observed in clinical trials for the most above named therapies; however, negative effect on male

fertility is expected for most of these drugs based on preclinical data including genotoxicity and mutagenicity studies (CYC, MMF, MTX, CS and tacrolimus). Spontaneous reports of drug-induced adverse effect on fertility have also been reported with drugs such as MTX. The clinical experience with enpatoran is limited and emerging safety profile of enpatoran is being evaluated in preclinical and clinical settings since enpatoran is in early development. However, based on known preclinical toxicology and clinical trial data, enpatoran offers a comparable safety profile with current standard of care therapy (for safety measures, refer to Section 2.3.1).

From the available data to date, enpatoran has been well-tolerated demonstrating no significant toxicity in healthy participants and has the potential to interfere with an overactive TLR7/8 pathway in SLE and CLE patients in this study. The highest dose to be evaluated in SLE/CLE participants is expected to result in exposure which will be below the exposure at no observed adverse effect level dose as determined from the enpatoran nonclinical toxicity evaluations. The compilation of data from the animal models and the Phase I study suggest that enpatoran effects on Type I IFN and cutaneous inflammation are expected to be observed within the 24-Week treatment period of the study in participants with these disease characteristics.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of enpatoran may be found below (Table 2) and in the IB.

Based on the available nonclinical data and the Phase I study data to date, the conduct of the study, as specified in this protocol, is considered justifiable.

2.3.1 Risk Assessment

The clinical experience with enpatoran is limited to 1 completed healthy participants (NCT03676322) study and 3 ongoing studies in healthy participants (NCT04880213) and in participants with Coronavirus Disease 2019 (COVID-19) pneumonia (NCT04448756) and SLE or CLE (NCT04647708). There is no similar class product available on the market. The following potential risks are being investigated based on the mechanism of action of a TLR7/8 antagonist and the nonclinical safety data of enpatoran (Table 2). All study participants will be made aware of signs and symptoms pertaining to contemplated potential risks and advised to report any adverse experiences throughout the study.

Table 2 Potential Risks of Clinical Significance

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Study Intervention	
Severe Infections (≥ Grade 3)	The potential exists for inhibition of TLR7/8 to increase the susceptibility to infection with ssRNA virus. No clinical experience of severe infection occurrence was reported in FIH study.	• Exclude participants with ongoing or active clinically significant viral, bacterial or fungal infection (see exclusion criteria). • Clinical evaluation for infection including SARS-CoV-2 (per local guidelines) before Day 1 of the dosing. Standard of care (SoC) vaccinations should be up to date as per local guidance.

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		• Participant education to identify signs and symptoms of infection to seek appropriate medical attention per institutional guidelines.
Seizure	Enpatoran has shown potential to cross the Blood Brain Barrier (BBB) in animal studies. Convulsions and severe behavioral changes were observed at dose levels exceeding the maximum tolerated dose i.e., 20 & 300 mg/kg/day in dog (13 weeks) and rat (4 weeks) toxicology studies, respectively. These CNS effects were not observed in 26 (rat) & 39 weeks (dog) repeat dose toxicity studies, in addition to the 13-Week repeat dose neurology study in dogs. No CNS toxicity was observed in a FIH study with doses up to 200 mg qd. Two adverse reactions (headache & dysgeusia; one participant each) were reported. Both AEs resolved spontaneously.	• Exclusion of participants with history of epilepsy or neurological disorders with seizure propensity. • Clinical evaluation including physical examination (with routine neurological examination), AE collection & assessment until End of Study (EOS). • Immediate discontinuation of study intervention if observed. • Participants (and caregivers) to be made aware of possible signs or symptoms of seizure to facilitate timely reporting and to seek medical attention appropriately.
Serotonin Syndrome	Based on enpatoran interaction with the 5-HT transporter (Study No.100032883 and 100033884), a potential for drug-induced serotonin syndrome is anticipated	• Exclude participants requiring regular use of medication associated with serotonin syndrome (see Section 5.2) • Identification of signs & symptoms of serotonin syndrome per clinical evaluation (The Hunter serotonin toxicity criteria [Dunkley 2003]) • Participants to be made aware of possible signs & symptoms to be reported immediately • Suspension of enpatoran administration upon occurrence of relevant signs and symptoms; discuss with Sponsor medical responsible.
Clinically significant Cardiac arrythmia	A transient but detectable QTc prolongation was observed in cardiovascular studies in guinea pigs and dogs. In the FIH study, no CVS toxicity or ECG findings were reported on Holter ECG recordings.	• Exclude participants with clinically significant ECG findings or unstable cardiovascular disease. • 12-Lead ECG monitoring throughout the study at specified time points & as indicated clinically. • Monitor closely asymptomatic QTc prolongation of clinically signification. • Medication associated with prolonged QTc should be suspended if appropriate for the duration of the study. • If clinically significant sign, symptom or ECG abnormality is observed, enpatoran may be suspended if appropriate.

Identified and Potential Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Impairment of male reproductive organs	In 13-weeks toxicity study in rats demonstrated a trend to reduced weights of prostate, epididymides and seminal vesicles (≥ 10 mg/kg/day), testis at high dose (100/60 mg/kg/day). Whereas, decreased prostate weight was shown in dogs. In 26-Week (rat) and 39-Week (dog) toxicology studies, a potential for decrease in ejaculate volume and sperm count and motility was demonstrated. Most of these findings recovered or showed ongoing recovery after an 8-Week dosing free period. Although there were no histopathological effects noted on the sperm at the end of the treatment period in dog study, a functional effect on male fertility could not be completely excluded. Based on the anticipated exposure levels in humans, the risk of similar adverse effects is expected to be low and temporary (reversed upon discontinuation of the study intervention) if any.	• Monitor clinically significant change in reproductive hormone levels in male study participants at protocol-specified time points. • Sperm donation is prohibited during the study until 90 days after the last dose of IMP. • Highly effective contraception method/s to be exercised by all study participants throughout the study. • As a precautionary measure, male participants may seek advice about the possibility of sperm preservation before initiation of study intervention, if appropriate.

AE = adverse event, CNS = central nervous system, ECG = electrocardiogram, EEG = electroencephalogram, FIH = first in human, 5-HT = 5-hydroxytryptamine, IFN = interferon, qd = once a day, NOAEL = no observed adverse effect level, QTc = QT interval corrected for heart rate, RNA = ribonucleic acid, SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2, ssRNA = single-stranded RNA, TLR(7/8) = Toll-Like Receptor (7 or 8).
* Participants will be made aware of the potential risk before obtaining ICF signature.

2.3.2 Risk Assessment in the Context of SARS-CoV-2

Frequent and ongoing detailed risk assessments of the impact of the COVID-19 pandemic on the study will be performed. A risk mitigation plan is in place, which takes into account current knowledge and also potential uncertainties. Details of the contingency plan for maintaining study activities, including site initiation, monitoring, and close-out activities, will be included in the study Clinical Monitoring Plan.

2.3.3 COVID-19 Vaccination

If a COVID-19 vaccine is intended to be used for a study participant during the study, the following guidance must be followed:

- COVID-19 vaccines should be authorized or approved by local Health Authorities and considered appropriate for immunosuppressed patients per local guidance.
- Administration of the COVID-19 vaccine timely after a scheduled visit (i.e., no later than 2 weeks after a study visit which are occurring every 4 weeks; for the visit of 2 weeks or the Day 1 visit, vaccination is allowed 1 week prior to the visit) is advised to minimize any potential impact on the study data collected at each visit.

Vaccination with a COVID-19 vaccine unauthorized and not approved by the country-specific health agencies or with a live or live attenuated virus vaccine is not permitted during the treatment period of the study.

2.3.4 Benefit Assessment

The candidate therapeutic being evaluated may or may not improve clinical outcome of an individual adult participant with SLE or CLE. While there may not be benefits for an individual participant, this study may help to further understand the immunopathogenesis of lupus and elucidate new pathways for treatment.

2.3.5 Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants in this study, the contemplated potential risks in association with enpatoran are justified by the anticipated benefits that may be afforded to participants with SLE or CLE.

3 Objectives and Estimands

Objectives	Estimand attributes
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: Patients with active SCLE, DLE or SLE with predominantly active lupus rash Note: Cohort A participants Treatment: Enpatoran vs placebo Intercurrent Event Strategy: • Early treatment discontinuation due to any reason: treatment policy • Protocol-prohibited medications, as determined by Endpoint Adjudication Committee (EAC): treatment policy • Corticosteroid use not compliant with protocol rules as determined by EAC: treatment policy 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.

Objectives	Estimand attributes
To evaluate the dose-response relationship of enpatoran in reducing disease activity based on BICLA response rate	Endpoint: BICLA response at Week 24
	Population: Patients with active SLE Note: Cohort B participants Treatment: Enpatoran vs placebo Intercurrent Event Strategy: • Early treatment discontinuation due to any reason will be considered as non-responder (composite estimand strategy) • Protocol-prohibited medications, as determined by EAC will be considered as non-responder (composite estimand strategy) • Corticosteroid use not compliant with protocol rules as determined by EAC will be considered as non-responder (composite estimand strategy) Population-Level Summary: Responder rates and 95% CI. The MCP-Mod procedure will be performed to evaluate the dose-response relationship
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)
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
	Population: Patients with active SCLE, DLE or SLE with active lupus rash Note: Active SCLE, DLE and SLE participants from Cohort A OR Cohort B with CLASI-A ≥ 8 at Screening and confirmed at Day 1 Intercurrent Event Strategy: • Early treatment discontinuation due to any reason: treatment policy • Protocol-prohibited medications, as determined by EAC: treatment policy • Corticosteroid use not compliant with protocol rules as determine by EAC: treatment policy Population-Level Summary: LS mean (SE) at each visit and treatment difference (95% CI) as estimated by MMRM

Objectives	Estimand attributes
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: Patients with active SLE (Cohort B participants) Intercurrent Event Strategy: same as BICLA response Population-Level Summary: same as BICLA response
To evaluate the efficacy in disease control of enpatoran compared to placebo in lupus participants with predominantly active lupus rash	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 • Occurrence of CLA-IGA 0 or 1 at Week 16 and Week 24
	Population: Patients with active SCLE, DLE or SLE with predominantly active lupus rash Note: Active SCLE, DLE and SLE participants from Cohort A Intercurrent Event Strategy: same as BICLA response Population-Level Summary: number and proportion with 95% CI of participants achieving the respective response definition at Week 12 and Week 24
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: Patients with active SLE Note: Cohort B participants Intercurrent Event Strategy: Same as BICLA response Population-Level Summary: Number and proportion with 95% CI of participants achieving the respective response definition at Week 12 and Week 24
	Endpoints: • Change in the number of joints which are tender and swollen in 28-joint count from baseline at Week 24 • Change from baseline in Physician's Global Assessment at Week 24

Objectives	Estimand attributes
	Population: as above Intercurrent Event Strategy: • Early treatment discontinuation due to any reason: treatment policy • Protocol-prohibited medications, as determined by EAC: treatment policy • Corticosteroid use not compliant with protocol rules as determine by EAC: treatment policy Population-Level Summary: Summary statistics at each visit
	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: as above Intercurrent Event Strategy: • Early treatment discontinuation: treatment policy • Protocol-prohibited medications, as determined by EAC: composite strategy Population-Level Summary: HR and CI from stratified Cox model using randomization strata according to IVRS/IWRS, Kaplan-Meier estimates
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 Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores at Week 24
	Population: Patients with active SCLE, DLE or SLE with active lupus rash. Note: Active SCLE, DLE and SLE participants from Cohort A OR Cohort B with CLASI-A ≥ 8 at Screening and confirmed at Day 1. Intercurrent Event Strategy: • Early treatment discontinuation due to any reason: treatment policy • Protocol-prohibited medications, as determined by EAC: treatment policy • Corticosteroid use not compliant with protocol rules as determine by EAC: treatment policy 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

Objectives	Estimand attributes
	Population: Patients with active SLE Note: Cohort B participants Intercurrent Event Strategy: • Early treatment discontinuation due to any reason: treatment policy • Protocol-prohibited medications, as determined by EAC: treatment policy • Corticosteroid use not compliant with protocol rules as determine by EAC: treatment policy Population-Level Summary: descriptive statistics at each visit and treatment difference at each study visit as estimated by MMRM
Exploratory	
To demonstrate the effect of enpatoran compared with placebo on changes in lupus rash disease activity over time	Endpoints: • Percent change from baseline in CLASI-A through Week 24 • CLASI-50 response through Week 24, defined as ≥ 50 % improvement from baseline in participants with CLASI-A ≥ 8 • Response through Week 24 defined as a ≥ 4-point reduction in CLASI-A score relative to baseline • Response through Week 24 defined as a ≥ 7-point reduction in CLASI-A score relative to baseline (Cohort A participants OR Cohort B SLE participants with CLASI-A ≥ 8 at Screening and confirmed at Day 1)
To evaluate the effect of enpatoran compared with placebo on changes on SLE disease activity over time in SLE participants in Cohort A	Endpoints: • Hybrid SELENA-SLEDAI change over time • Change from baseline in Physician's Global Assessment at Week 16 and 24 (Cohort A SLE participants)

Objectives	Estimand attributes

To demonstrate the effect of enpatoran compared with placebo on changes in SLE disease activity over time	Endpoints:
	• Time to first SRI-4 response sustained through Week 24
	• Time to first BICLA response sustained through Week 24
	• SRI-5, -6, -7 and -8 response from Day 1 through Week 24
	  ○ For SRI-5: ≥ 5-point reduction in hybrid SELENA-SLEDAI score
	  ○ For SRI-6: ≥ 6-point reduction in hybrid SELENA-SLEDAI score
	  ○ For SRI-7: ≥ 7-point reduction in hybrid SELENA-SLEDAI score
	  ○ For SRI-8: ≥ 8-point reduction in hybrid SELENA-SLEDAI score
	• Change in total and in organ specific hybrid SELENA-SLEDAI scores from Day 1 through Week 24
	• Change in organ specific BILAG score (using validated numerical score) from Day 1 through Week 24
	• Change in proteinuria (UPCR by spot urine collection) from Day 1 through Week 24
	
	(Cohort B participants)

To demonstrate the efficacy of enpatoran compared with placebo in reducing disease activity in SLE participants who are serologically active* *Serologically active is defined as having one or more of the following at Day 1: • Positive anti-dsDNA antibodies: positive anti-dsDNA ≥ 15 IU/mL at Day 1 • Low C3: C3 < 0.9 g/L at Day 1 • Low C4: C4 < 0.1 g/L at Day 1	Endpoints: • BICLA response at Week 24 • SRI-4 response at Week 24 (Cohort B participants)

To demonstrate the effect of enpatoran compared with placebo on achieving both SRI response and clinically meaningful CS reduction in SLE participants on prednisone ≥ 10 mg at Day 1	Endpoints:
	• SRI-4, -5, -6, -7, or -8 response and clinically meaningful CS reduction, defined as meeting both of the following:
	  • 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
	  • No new BILAG A organ domain scores and no more than 1 new BILAG B organ domain score during Weeks 13 through 24
	
	(Cohort B participants)

To demonstrate effect of enpatoran compared with placebo on CS usage	Endpoint: • Change in prednisone-equivalent CS daily dose from Day 1 through Week 24 • Cumulative prednisone-equivalent CS dose (Cohort A OR Cohort B participants)

Objectives	Estimand attributes
To evaluate the vaccine immunization status compared with placebo	Endpoint: Antibody titers to tetanus toxoid, diphtheria toxoid, SARS-CoV-2 antigens and selected pneumococcal antigens at baseline and Week 24 EOT/early termination visit
Evaluate the association of enpatoran response (efficacy) with baseline biomarker status	In participants with baseline biomarker status: Group 1 ([IFN-GS high AND/OR positive RNA auto-antibodies: anti-SSA/Ro, SSB/La, Smith/RNP] vs [IFN-GS low AND negative RNA auto-antibodies: anti-SSA/Ro, SSB/La, Smith/RNP]) or Group 2 (IFN-GS high vs IFN-GS low) Endpoints: • BICLA response from Day 1 through Week 24 (SLE in Cohort B only) • SRI-4 response from Day 1 through Week 24 (SLE in Cohort B only) • Percent change from baseline in CLASI-A through Week 24 (Cohort A participants OR Cohort B SLE participants with CLASI-A ≥ 8 at Screening and confirmed at Day 1)
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 photosensitivity domain score at each study visit. • Change from Baseline in Itch Numeric Rating Scale (NRS) score at each study visit • Change from Baseline in the Patient Global Assessment of lupus skin symptom severity (Skin PtGA) at selected study visits • Patient Global Impression of Change in lupus skin symptom severity (Skin PGIC) at selected study visits • Change from Baseline in the Medical Outcome Study (MOS) Sleep (acute version) domain scores at Week 12 and Week 24 (Cohort A participants OR Cohort B SLE participants with CLASI-A ≥ 8 at Screening and confirmed at Day 1)

Objectives	Estimand attributes
To evaluate the efficacy of enpatoran compared to placebo in patient-reported symptoms and functional status, in participants with active SLE	Endpoints: • Change from Baseline in the Lupus Symptom Severity Diary individual item numeric rating scale scores at each study visit • Change from Baseline in Patient Global Assessment of lupus symptom severity (PtGA) at selected study visits • Patient Global Impression of Change in lupus symptom severity (PGIC) at selected study visits • Change from Baseline in the PROMIS Physical Function 10a scores at Week 12 and Week 24 • Change from Baseline in the Medical Outcome Study (MOS) Sleep scale domain scores at Week 12 and Week 24 (Cohort B participants)
To evaluate the efficacy of enpatoran compared to placebo in cognitive function, in participants with active SLE	Endpoints: • The Montreal Cognitive Assessment (MoCA) test scores at Day 1 and selected visits • Change from Baseline in MoCA test scores at selected visits (Cohort B participants with MoCA test scores at Screening, based on age-adjusted norms)
To investigate the effect of enpatoran on biomarkers in participants with active SLE	Endpoints: • Change in serum C3 levels from Day 1 through end of study in participants with low levels of C3 at Screening. • Change in serum C4 levels from Day 1 through end of study in participants with low levels of C4 at Screening. • Change in anti-dsDNA antibody levels from Day 1 through end of study in participants with positive anti-dsDNA antibodies at Screening. (Cohort B participants)
To investigate the effect of enpatoran on immune cell subsets and immunoglobulins.	Endpoints: • Change in immune cell subsets from Day 1 through end of study. • Change in serum Ig levels (IgG, IgA, IgM) from Day 1 through end of study
To investigate the effect of enpatoran on PD biomarkers.	Endpoints: • Change in serum biomarkers (e.g., cytokines, autoantibodies) from Day 1 through end of study. • Change in gene expression (e.g., IFN-GS) from Day 1 through end of study. • Change in biomarkers (e.g. MxA, IFN-GS) in skin biopsies from Day 1 through Week 4

Objectives	Estimand attributes
To collect enpatoran plasma concentration data via sparse PK sampling to contribute to population PK and exposure-response analyses of PD biomarker (e.g. IFN-GS) and/or efficacy (e.g. CLASI-A, BICLA) and safety of enpatoran	Endpoints: Enpatoran plasma concentrations, e.g. Ctrough (Integrated) Population PK and exposure-response results will be reported separately in a stand-alone report, as it may also include data from other studies. Exploratory analyses of circulating metabolites of enpatoran, in plasma, may be conducted
To collect DNA and explore gene analysis	An exploratory evaluation of correlations between DNA germline polymorphisms and PK, study intervention benefit, and AEs may be conducted and documented

4 Study Design

4.1 Overall Design

This is a global, Phase II, basket proof-of-concept and dose-finding, randomized, double-blind, placebo-controlled, dose-ranging, parallel and adaptive multicenter study in participants with active SLE or CLE (active SCLE and/or DLE) treated with standard of care to evaluate the efficacy and safety of enpatoran administered orally twice per day for 24 weeks.

The planned total duration of the study for each participant will be up to approximately 33 weeks: up to a 7-Week Screening Period (5-Week Screening Period with the possibility to expand by an additional 2 weeks if needed to repeat a laboratory test or due to an unanticipated event), a 24-Week Double-Blind Placebo-Controlled (DBPC) Treatment Period followed by a 2-Week Safety Follow-up Period. Upon completion of the eligibility form, and confirmation of eligibility of active SLE, (active SCLE and/or DLE) by the Medical Monitor as well as Primary Investigator assessment that participant continues to meet inclusion/exclusion criteria, the participant will be randomized. The study will be conducted on an outpatient basis.

The study consists of 2 cohorts to establish PoC and dose-finding for enpatoran in 2 patient populations: Cohort A and Cohort B. Cohort B has a dose-finding adaptive design comprised of Part 1and Part 2. Cohort A and Cohort B Part 1 will start in parallel with a subsequent initiation of Cohort B Part 2.

- Cohort A will have participants with CLE (active SCLE and/or DLE) (CLASI-A ≥ 8) or SLE with predominantly active lupus rash (CLASI-A ≥ 8) and for SLE mild or no extra-mucocutaneous disease activity (BILAG 2004 1B, C, D [i.e., No BILAG 2004 A and No BILAG 2004 ≥ 2B]). Approximately 100 participants will be randomized 1:1:1:1 to enpatoran 25 mg twice per day (n=25): enpatoran 50 mg twice per day (n=25): enpatoran 100 mg twice per day (n=25): placebo twice per day (n=25).
- Cohort B will have SLE participants who have moderate to high systemic disease activity (BILAG A and/or 2B) with 1 or 2 of the following: CLASI-A ≥ 8 and/or SLEDAI ≥ 6. An adaptive design will be used for this cohort: Part 1 is designed to assess a clinical signal and based on an interim analysis of Part 1; Part 2 may be adapted to improve dose-finding in SLE if needed.
    - Part 1 will be initiated first with approximately 60 participants randomized 2:1 to enpatoran 100 mg twice per day vs placebo to evaluate the futility of enpatoran vs placebo in SLE participants.
    - Part 2 will be initiated after approximately 60 participants have been enrolled in Part 1 and participants will be randomized 1:1:1:1 to enpatoran 25 mg twice per day: enpatoran 50 mg twice per day: enpatoran 100 mg twice per day: placebo twice per day. An interim analysis is planned when 60 participants from Cohort B Part 1 complete at least 12 weeks of treatment, or discontinue early, and will inform potential adaptations of dose and randomization ratio for Part 2 (maximum of 4 dose levels; see Section 4.3), if needed, or the decision to terminate Cohort B for futility. Participants from Cohort B will continue on their dose level initiated prior to any potential adaptation until completion of study treatment at Week 24 unless Cohort B

is terminated for futility. Total sample size of Cohort B will not exceed 340 participants.

This study has interim analyses planned for Cohort A and B (see Section 9.4.4).

Participants will self-administer study intervention twice per day at a set time each day unless a study visit day is planned. On scheduled study visit days, study intervention will be administered on site after the scheduled pre-dose study assessment/procedures have been performed.

Protocol-specified corticosteroid tapering guidance and targets will be implemented in this study (see Section 6.8.1 and Appendix 7). Sites will be instructed to follow this guidance and must taper corticosteroids.

Participants who discontinue treatment are encouraged to remain in the study and follow the scheduled study visits after completion of the ET assessments as soon as possible and revert to the same study schedule (Table 1) based on the participant's Day 1 visit until the Safety follow-up visits are completed. In case of study withdrawal, the ET Study Visit must occur as soon as possible and will replace the EOT Visit (and must subsequently be followed by Safety follow-up visits).

Participants who complete the 24-Week DBPC Treatment Period may be offered participation in an optional long-term extension (LTE) study as part of a separate protocol.

Special oversight committees will include External Independent Data Monitoring Committee, Study Steering Committee, Endpoint Adjudication Committee and Firewall team. The Firewall team will be composed of a restricted group of individuals within the Sponsor team who are not directly involved in the study conduct activities.

4.2 Scientific Rationale for Study Design

TLR7 and TLR8 are activated by ssRNA, which is found in immune complexes present in SLE and CLE patients. Activation of TLR7 and TLR8 leads to release of cytokines including type I IFN, IL-6 and TNFα (Barrat 2005). A central role for cytokines and in particular type I IFN in lupus pathogenesis is supported by abundant data from SLE and CLE patients as well as murine lupus disease models (Furie 2019, Morand 2019, Furie 2020, Robinson 2015, Werth 2020). The present basket study is designed to establish PoC and dose-finding (DF) by evaluating the efficacy, safety, PK and PD (e.g., TLR7 and TLR8-induced cytokines, IFN-GS, etc.) of enpatoran tablets taken by mouth twice per day for 24 weeks during the DBPC treatment period. The study design is informed by the data on enpatoran obtained in the Phase I FIH study (NCT03676322), from animal model experiments (refer to IB), and from publicly available results from clinical studies of other IFN-suppressive agents in SLE.

Double-blind treatment within each cohort will be used to reduce potential bias during data collection and assessment of AEs, from both study staff and participants.

Participants receiving placebo or enpatoran will also receive standard of care with some predefined limitations (see Sections 6.8.1, 6.8.2 and 6.8.4).

In Cohort A, a randomization in a 1:1:1:1 ratio over 4 dose levels will be used to minimize bias in the assignment of study participants to treatment groups and to increase the likelihood that known and unknown participant attributes (e.g., demographic and baseline characteristics) are

evenly balanced across treatment groups. In the 2-stage Cohort B, randomization will start with a ratio of 2:1 over 2 dose levels (enpatoran vs placebo) in Part 1, followed by a randomization in a 1:1:1:1 ratio over 4 dose levels in Part 2. Cohort B is designed to allow planned adaptations of enpatoran dose range and randomization ratio based on new information becoming available after this study has started (see Section 4.3).

Percent change from baseline in CLASI-A scores at Week 16 is the primary endpoint for participants with CLE (active SCLE and/or DLE) or SLE and CLASI-A score ≥ 8 at baseline. The activity score of CLASI correlates with changes in clinical validation measures related to skin health, pain and itch and can be used to identify clinically significant improvements in cutaneous lupus disease activity (Bonilla-Martinez 2008, Klein 2011).

BICLA response at Week 24 is the primary endpoint for participants with active SLE. BICLA requires clinically meaningful partial improvement but improvement is required in all organs and may be less sensitive than SRI in determining clinically significant improvement in SLE disease activity, particularly patients with multi-organ involvement (Thanou 2014).

4.3 Justification for Dose

To evaluate the treatment effect and dose-exposure-response relationships for efficacy and safety of enpatoran in CLE (active SCLE and/or DLE) and SLE patients on stable background (SoC) therapy, the following dosing regimens are proposed to be investigated in Cohort A over a treatment duration of at least 24 weeks: 25, 50 and 100 mg enpatoran twice per day administered orally in a tablet formulation without food restriction.

Cohort B has an adaptive 2-stage dose-finding design and is designed to allow for planned enpatoran dose-range and randomization ratio adaptations based on observed data at interim analysis as well as relevant information becoming available after the Phase II study start (e.g., from the ongoing Phase Ib study NCT04647708). The adaptive design may improve dose-finding by allowing to explore alternative dose levels, yielding more informative dose-response data (see Section 9.4.4). Cohort B is comprised of Part 1 and subsequent Part 2. In Cohort B Part 1, enpatoran 100 mg twice per day will be compared with placebo to determine futility of the treatment effect. The proposed dose levels in Cohort A and Cohort B Part 1 are selected based on the joint evaluation of clinical PK, PD, and safety data obtained in the FIH study in healthy participants (NCT0367632) and guided based on non-clinical safety and efficacy data (see below).

Cohort B Part 2 will be initiated when approximately 60 participants have been enrolled in Part 1. Cohort B Part 2 doses will be initiated as enpatoran 25, 50 and 100 mg enpatoran twice per day compared to placebo and will be adapted, if needed, based on the totality of available clinical safety, efficacy, and dose-exposure-response data from this Phase II study at the planned interim analyses (as described in Section 9.4.4) and other enpatoran clinical studies and without exceeding exposures at the highest clinically investigated dose.

Preclinical in vivo efficacy in mouse models of Lupus disease together with PK/PD target engagement data obtained in C57/BL6 mice were used to define the following PD targets: (i) for anticipated minimum efficacy: enpatoran concentrations that inhibit 60% of IL-6 cytokine release (IC_{60}) throughout the dosing interval (trough concentrations, $C_{min,ss} > IC_{60}$), and (ii) for > 50% IFN-GS suppression: enpatoran concentrations that maintain 90% inhibition of IL-6

release (IC_{90}) throughout the dosing interval ($C_{min,ss} > IC_{90}$). Population modeling of PK/PD data from the FIH study was used to inform the phase II dose selection in patients; three dose levels are selected to explore the anticipated therapeutic effect of enpatoran, covering a wide range of $C_{min,ss}$ with minimum overlap between the dose groups. Under 25 mg enpatoran twice daily > 50% of participants are expected to achieve the IC_{60} target for inhibition of ex vivo IL-6 release; doses of 50 and 100 mg twice daily are proposed to maximize the number of participants above IC_{60} and IC_{90} targets for IL6 (at 100 mg twice daily almost 90% participants are expected to achieve IC_{90} target coverage).

The FIH study in healthy participants evaluated an oral M5049 solution. Pharmacokinetic results indicated dose-proportionality of maximal concentrations and overall exposure (AUC) in the investigated dose range (1 to 200 mg single or as daily dose) with a terminal half-life of 7 to 11 hours. The AUC was increased by 33% and C_{max} was decreased by 11% under fed condition compared to fasted conditions as observed in a small food effect cohort. M5049 has been well-tolerated and has not demonstrated any toxicity in healthy participants (FIH study). Preliminary concentration-QT analysis of FIH PK and electrocardiogram (ECG) data (collected by digital Holter ECG) with linear mixed effect model did not show any significant prolongation effect on QT-interval of M5049 administered as single-dose or repeat daily doses up to 200 mg. The expected total $AUC_{0-24h,ss}$ and $C_{max,ss}$ of the proposed doses remain below the total exposures at the no observed adverse effect level (NOAEL) in the 26-Week (Study ID: 36835) and 39-Week (Study ID: 36836) nonclinical toxicology studies in rat and dog (Safety margins: 25 mg twice daily, ≥16.8-fold $AUC_{0-24h,ss}$ and $C_{max,ss}$; 100 mg twice daily, ≥ 4.2-fold $AUC_{0-24h,ss}$ and $C_{max,ss}$).

The current study will use an immediate-release tablet formulation without food restriction. Enpatoran is considered as a Biopharmaceutics Classification System Class 1 compound and tablet formulation showed very rapid dissolution profile. It is expected that oral administration of enpatoran using the tablet formulation would generate similar exposures as the solution administered in the FIH study. The same tablet formulation (25 mg strength) is used without food restriction in ongoing clinical studies (NCT04448756; NCT04647708; NCT04880213). The potential for ethnic sensitivity is currently being investigated in an ongoing clinical study assessing the safety, tolerability, PK and PD in Japanese and Caucasian healthy volunteers (NCT04880213). The observed comparability between Japanese and Caucasian in the latter study is intended to also inform about ethnic in/sensitivity for other Asian populations (e.g., Chinese, Korean). Based on the results of the ethno-bridging study, Asian participants may be included into the proposed Phase II study.

Based on the above considerations, the proposed enpatoran doses in this Phase II study should provide the opportunity to evaluate a treatment effect and dose-exposure-response relationships for efficacy and safety in each indication, SLE and CLE, with acceptable safety margins. Refer to the IB for further details.

4.4 End of Study Definition

A participant has completed the study if he/she has completed all study parts, including the last scheduled procedure shown in the Schedule of Activities (SoA; see Table 1).

The end of the study is defined as the date of the last scheduled procedure shown in the SoA (see Table 1) for the last participant in the study.

The study may not be considered closed as long as:

- Any participant is still receiving any study intervention.
- Visits specified by the protocol are still taking place.
- Procedures or interventions according to the protocol are still being undertaken in any participant.
- The post-intervention Follow-up Period, defined in the clinical study protocol as being part of the study, has not yet been completed for any participant.

Appendix 2 provides details related to study closure and site termination.

5 Study Population

The criteria in Sections 5.1 and 5.2 are designed to enroll only participants, who are appropriate for the study; thereby, ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions are considered when deciding whether a participant is suitable for this study.

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

Before performing any study assessments that are not part of the participant's routine medical care, the Investigator will confirm that the participant or the participant's legal representative has provided written informed consent, as indicated in Appendix 2.

Eligibility will be evaluated by the study Investigator, and re-evaluated and confirmed by the Sponsor or designee Medical Monitors comprising the study eligibility team. Additional lupus experts may be consulted during the eligibility process (e.g., to confirm CLE subtypes diagnosis). Sites will be required to submit an eligibility packet (consisting of an eligibility checklist and appropriate documentation) for consented and potential eligible participants. The participant's eligibility will be assessed at a Screening Visit, which will occur up to 5 weeks prior to the Randomization Visit (Day 1). When a laboratory test must be repeated during the Screening Period or an unanticipated event occurs, the Screening Period can be extended to 7 weeks after discussion with the Medical Monitor. See Table 1 for a list of assessments performed at Screening to determine the eligibility of the participant to take part in the study. Participants will be randomized into the study when eligibility is confirmed.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Age

1. Are ≥ 18 to ≤ 75 years of age at the time of signing the informed consent. If participants are enrolled in Japan, if a participant is < 20 years of age, the written informed consent from the participant's parent or guardian will be required in addition to the participant's written consent for this country.

Vaccinations

2. Are up to date, according to local guidelines, with vaccination against Streptococcus pneumoniae and influenza virus (as seasonally required for influenza virus).

Active SCLE and/or DLE (Cohort A)

3. Diagnosis of SCLE or DLE documented in medical history. Predominant findings of active lupus rash must be SCLE and/or DLE, but other skin manifestations of CLE will be allowed (e.g., lupus tumidus, Acute Cutaneous Lupus Erythematosus [ACLE], etc) on a case-by-case basis if their main diagnosis is active SCLE and/or DLE. Diagnosis must include one of the following options:
   a. Historical skin biopsy (i.e., pathology report; punch or shave biopsy) within 10 years prior to Screening visit and confirmation of current diagnosis by skin photography at Screening visit.

      OR

   b. Fresh punch skin biopsy at Screening visit.

      OR

   c. If target lesion is unsuitable for biopsy (e.g., malar rash, bridge of the nose, scalp), skin photography at Screening visit may be allowed on a case-by-case basis.
4. Disease duration of ≥ 6 months from time of diagnosis to Screening.
5. CLASI-A ≥ 8 at Screening Visit; this must be confirmed at Day 1 Visit.

Active SLE

6. Diagnosis of SLE and fulfil Systemic Lupus International Collaborating Clinics (SLICC) classification criteria (Petri 2006), and/or ≥ 4 ACR classification criteria (Hochberg 1997) and/or EULAR/ACR 2019 classification criteria (Aringer 2019).
7. Disease duration of ≥ 6 months from when participant met 2012 SLICC, and/or 1997 ACR (Hochberg 1997), and/or 2019 EULAR/ACR classification criteria for SLE until Screening Visit.
8. Positive test results for ANA (human epithelial cell-2 ANA ≥ 1:80) and/or anti-dsDNA antibody (≥ 15 IU/mL) and/or anti-Smith antibody during Screening Period.
9. Presence of either Scenario 1 OR Scenario 2 (See Figure 1).

Scenario 1 (Cohort A – predominantly active lupus rash):

- Cutaneous lupus erythematosus disease area and activity index (CLASI-A) ≥ 8 at Screening Visit and confirmed at Day 1 Visit.

  AND

- British Isles Lupus Assessment Group (BILAG 2004) 1B, C, D (i.e., No BILAG 2004 A and No BILAG 2004 ≥ 2B) at Screening visit.

OR

Scenario 2 (Cohort B – moderate to high systemic disease activity):

- BILAG 2004 ≥ 1A or 2B at Screening Visit;

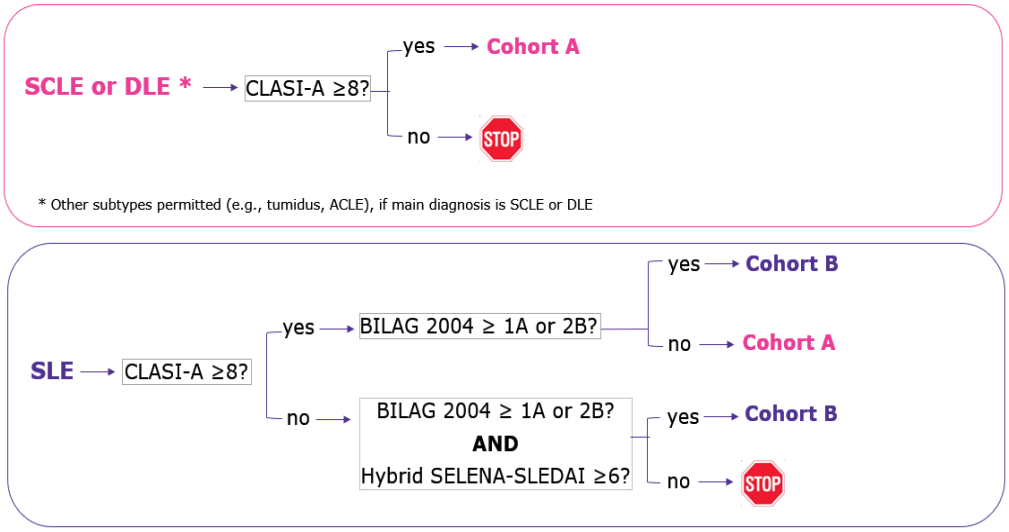
AND 1 or 2 of the following:

a) Hybrid SELENA-SLEDAI ≥ 6 at Screening Visit and confirmed clinical hybrid SELENA-SLEDAI ≥4 (excluding laboratory parameters) at Day 1 Visit.

   AND/OR

b) CLASI-A ≥ 8 at Screening Visit and confirmed at Day 1 Visit.

Figure 2 **Assignment of Study Cohort Based on Disease Activity Features at Screening visit**



See Cohort A and B classification guideline above.

Stop indicates not eligible for this study

ACLE = Acute cutaneous lupus erythematosus, BILAG = British Isles Lupus Assessment Group, CALSI-A = Cutaneous Lupus Erythematosus Disease Area and Severity Index-A, DLE = Discoid lupus erythematosus, SCLE = Subacute cutaneous lupus erythematosus, SLE = Systemic lupus erythematosus, SELENA = Safety of Estrogens in Systemic Lupus Erythematosus National Assessment, SLEDAI = Systemic Lupus Erythematosus Disease Activity Index.

Weight

10. Have a body mass index within the range 18.5 to 35.0 kg/m^2 (inclusive).

Sex

11. Are male or female at birth.

12. Contraceptive use by males or females will be consistent with local regulations on contraception methods for those participating in clinical studies.

a. Female participant:

- Is not breastfeeding.
- Is not pregnant (i.e., has a negative serum pregnancy test, as required by local regulations, within 24 hours before the first dose of study intervention).

  Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.4.

- **Not** a Woman of childbearing potential (WOCBP).
- If a WOCBP, use a highly effective contraceptive method (i.e., with a failure rate of <1% per year), preferably with low user dependency (two methods may be considered to achieve optimal results i.e. <1% failure rate per year), as described in Appendix 3 for the following time periods:

- Before the first dose of the study intervention, if using hormonal contraception:
  - Has completed at least one 4-Week cycle of an oral contraception pill and either had or has begun her menses.

  OR

  - Has used a depot contraceptive or extended-cycle oral contraceptive for least 28 days and has a documented negative pregnancy test using a highly sensitive assay.

  AND

  - A barrier method, as described in Appendix 3.

- During the intervention period.
- After the study intervention period (i.e., after the last dose of study intervention is administered): for at least 90 days after the last dose of study intervention and agree not to donate eggs (ova, oocytes) for reproduction during this period.

The Investigator evaluates the appropriateness and effectiveness of the contraceptive method in relationship to the first dose of study intervention.

Note: Estrogen-containing hormonal contraceptives are contraindicated in this study.

The Investigator reviews the medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female with an early undetected pregnancy.

b. Male Participants:

Agree to the following during the study until at least 90 days (a spermatogenesis cycle) after the last dose of study intervention.

- Refrain from donating fresh unwashed semen.

PLUS, either:

- Abstain from any activity that allows for exposure to ejaculate.

OR

- Use a male condom:
  - When having sexual intercourse with a WOCBP, who is not currently pregnant, and instruct her to use a highly effective method with a failure rate of <1% per year, as described in Appendix 3, since a condom may break or leak.
  - When engaging in any activity that allows for exposure to ejaculate.

13. Currently receiving a stable dose of at least one of the following standards of care therapies for lupus:
    a. Immunomodulator/immunosuppressant (antimalarial, methotrexate, 6-mercaptopurine, sulfasalazine, mycophenolate mofetil or sodium, azathioprine, tacrolimus, leflunomide, dapsone, or retinoids) ≥ 4 weeks prior to Screening Period.
    b. Oral corticosteroids ≥ 2 weeks prior to Screening Period.
    c. Topical corticosteroids ≥ 2 weeks prior to Screening Period.

Informed Consent

14. Capable of giving signed informed consent, as indicated in Appendix 2, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and this protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Primary diagnosis of autoimmune or rheumatic disease other than SLE or CLE (discuss with Medical Monitor if overlap syndrome). Note: Secondary Sjögren's syndrome or an autoimmune thyroiditis are not exclusionary.
2. Drug-induced lupus (SLE or CLE).
3. Any condition including dermatological diseases other than cutaneous manifestations of SLE or CLE (e.g., psoriasis), or any uncontrolled disease (e.g., asthma, interstitial lung disease, pulmonary arterial hypertension, morbid obesity), that in Investigator's or

Sponsor/designee's opinion constitutes inappropriate risk or contraindication for participation.

4. Active lupus nephritis on induction therapy, or induction therapy completed within 3 months of Screening visit (stable maintenance therapy with mycophenolate or azathioprine allowed).
5. Urine protein: creatinine ratio (UPCR) > 4 mg/mg (> 339 mg/mmol), and/or estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m^2 as calculated by the Modification of Diet in Renal Disease equation by the central laboratory:

   eGFR = 175 × (serum creatinine in mg/dL)$^{-1.154}$ × (age in years)$^{-0.203}$ × 0.742 (if female) × 1.212 (if race is black).
6. Any active signs, symptoms or diagnoses considered related to central nervous system (CNS) lupus within past 3 months or any history of uncontrolled seizures.
7. Any other history of epilepsy, other neurological disorder with seizure propensity, or neuropsychiatric conditions that may interfere with study evaluations.
8. Significant cardiovascular events (e.g., acute myocardial infarction, unstable angina or peripheral vascular disease symptoms, hospitalization for congestive heart failure, uncontrolled or New York Heart Association Class 3 or 4 congestive heart failure, cardiac surgery, ischemic or hemorrhagic stroke, or transient ischemic attack), ≤ 6 months before Screening Visit.
9. Active cardiac arrhythmia or clinically significant abnormality on ECG at Screening Visit or Day 1 that in the Investigator's or Sponsor/designee's opinion constitutes inappropriate risk or contraindication for study participation or could interfere with study objectives, conduct or evaluation (included but not limited to long QT syndrome, Wolff Parkinson White syndrome, or a malignant ventricular arrhythmia [e.g., ventricular fibrillation or tachycardia] unless treated). Note: any sinus bradycardia or tachycardia detected in the ECG will not be exclusionary unless other ECG abnormalities are identified.
10. Significant suicide risk in the last year (including suicidal ideation and/or suicidal behavior on the Columbia-Suicide Severity Rating Scale [C-SSRS] during Screening or Day 1).
11. History of or planned renal or solid organ transplant.
12. Ongoing or active clinically significant viral (including SARS-CoV-2), bacterial or fungal infection, or any major episode of infection requiring hospitalization or treatment with parenteral anti-infectives ≤ 4 weeks prior to or during Screening Period, or completion of oral anti-infectives ≤ 2 weeks prior to Screening Visit. Vaginal candidiasis, onychomycosis, and genital or oral herpes simplex virus considered to be sufficiently controlled will not be exclusionary.

    - Investigators should follow their local guidelines for SARS-CoV-2 testing during the Screening period (e.g., asymptomatic testing is required before entering a research study, symptomatic/exposure-based screening only, etc.,). In addition, within 3 to 5 days prior to randomization, all participants should be specifically questioned for coronavirus infectious disease due to SARS-CoV-2 symptoms or close contact with

someone known to have SARS-CoV-2 infection to determine if SARS-CoV-2 testing (accepted according to local guidelines) should be performed (or repeated).

- If required by local guidelines, a test for SARS-CoV-2 is needed for participants **before** the Screening visit.

13. Any of the following:

    a. A positive human immunodeficiency virus (HIV) test.

    b. Positive hepatitis C virus (HCV) antibody (Ab) and detectable HCV RNA nucleic acid amplification testing (NAAT) performed reflexively at Screening, *or* history of treated HCV with detectable HCV RNA NAAT performed reflexively at Screening.

    c. Positive hepatitis B virus (HBV) surface antigen, *or* positive HBV core Ab with negative HBV surface Ab and reflexive detectable HBV DNA NAAT at Screening, *or* no history of HBV vaccination with positive HBV surface and core Abs and reflexive detectable HBV DNA NAAT at Screening.

14. Any of the following:

    a. History of active tuberculosis (TB).

       Note: patients with a history of active or latent TB who have documented evidence of appropriate treatment and with no history of re-exposure since their treatment was completed would not be required to undergo the protocol specific TB testing for PPD, QuantiFERON test or T-SPOT test, but would still require a baseline chest x-ray to rule out active TB and documentation of completed treatment".

    b. Current diagnosis of active TB.

    c. Untreated latent TB infection (LTBI).

    d. Undergoing current treatment for LTBI.

    e. Participants with current household contacts with active TB.

In the absence of an active TB diagnosis, or clinical features consistent with an active TB diagnosis, LTBI is determined by any of the following:

- Prior TB skin test with purified protein derivative with induration ≥ 5 mm (unless vaccinated with Bacille Calmette-Guérin).
- Prior positive T-SPOT.TB (Elispot) result.
- Positive QuantiFERON test, either at Screening or with documented past results.

Note: All participants, except those who have previously completed appropriate and documented LTBI treatment, must undergo QuantiFERON testing during Screening. Participants with indeterminate or positive QuantiFERON results that may represent a false positive result by the Investigator with no clinical features consistent with active TB, will be evaluated with either a repeat QuantiFERON test or a T-SPOT.TB at the request of the Investigator. In the case of a negative QuantiFERON or T-SPOT.TB result, the participant may be enrolled after approval by the study eligibility team. If the repeat QuantiFERON result is indeterminate, the participant will be excluded.

15. History of malignancy (hematologic or solid tumor) ≤ 10 years prior to Screening Visit, except adequately treated basal cell or squamous cell carcinomas of the skin (≤ 3 lesions requiring treatment in lifetime) or adequately treated carcinoma in situ/cervical intraepithelial neoplasia of the uterine cervix.
16. Any major surgery such as abdominal, thoracic, or joint replacement surgeries ≤ 6 weeks prior to Screening Visit or planned major surgery during the study (including Follow-up).
17. History of alcohol or drug abuse ≤ 1 year prior to Screening Visit as per Investigator opinion.
18. History of splenectomy or functional asplenia.
19. Any condition that could interfere with study objectives, conduct, or evaluation in the opinion of the Investigator or Sponsor/designee.

Prior/Concomitant Therapy (See Appendix 6 for further details)

20. Known hypersensitivity to any study intervention, component, or placebo.
21. Initiation or dose change of anticoagulation or antiplatelet therapy ≤ 4 weeks prior to Screening Period.
22. Use of the following medications associated with aldehyde oxygenase (AOX) inhibition ≤ 4 weeks prior to Screening: raloxifene, tamoxifen, estradiol and derivatives, quetiapine. Female lupus participants who are taking estrogen-containing contraceptives will require switching to an alternative contraceptive method during the Screening period (≥ 4 weeks prior to Day 1) and should be discussed with the Medical Monitor.
23. Use of the following medications associated with serotonin syndrome prior to the Screening visit, unless otherwise specified:
    a. Antidepressants: Selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, St. John's wort, lithium (3 weeks prior to Screening) and fluoxetine (8 weeks prior to Screening).
    b. Analgesics: Tramadol, pethidine, fentanyl, dextromethorphan (e.g., in OTC cough remedies)
    c. Antiemetics: Ondansetron, metoclopramide
    d. Antibiotics: Linezolid, tedizolid
    e. Tryptophan
    f. Anxiolytic: Buspirone
    g. Methylthioninium chloride (methylene 75 blue)
24. Medications that are known to lower the seizure threshold. Participants taking such medications will be considered on a case-by-case basis.

25. The use, initiation, or dose change in the following therapies ≤ 2 weeks prior to Screening:
    a. Use of CS exceeding 30 mg daily prednisone-equivalent for SLE and CLE (SCLE and/or DLE), including but not limited to oral, topical corticosteroids Class IV, intramuscular, or injectable CS (Table 11).
    b. Use of topical calcineurin inhibitors more than one time per day.
    c. Initiation or dose change of angiotensin-converting enzyme inhibitors or angiotensin receptor blocker, or nonsteroidal anti-inflammatory drugs (NSAIDs), or use of NSAIDs above maximum prescribed dose per local label.
    d. Vaccination with a subunit or inactivated vaccine, excluding SARS-CoV-2 vaccine or vaccine series (See Section 2.3.3). Vaccination for influenza virus and S. pneumoniae is allowed during Screening, providing that vaccination completes at least 2 weeks before the Day 1 Visit.
26. The initiation, use, or change in the following therapies ≤ 4 weeks prior to Screening:
    a. Vaccination with live or live attenuated virus vaccine.
    b. Use of thalidomide or lenalidomide.
    c. Use of intralesional therapies.
    d. Use of tripterygium and total glucosides of paeony.
27. The initiation, use of a dose exceeding the maximum specified dose (see Appendix 6), or change in therapies < 8 weeks prior to Screening for any medication considered to have immunomodulating and/or immunosuppressant properties (e.g., antimalarials, methotrexate, 6-mercaptopurine, sulfasalazine, mycophenolate mofetil or sodium, azathioprine, dapsone, or retinoids). A stable dose of leflunomide is not exclusionary; however, participants having changed their dose or discontinued leflunomide must have done so at least 8 weeks prior to Screening.
28. The initiation, use or change in the following therapies ≤ 12 weeks prior to Screening:
    a. Use of abatacept, antitumor necrosis factor alpha agents, intravenous Ig, plasmapheresis, cyclophosphamide, or other disease modifying, immunosuppressive or immunomodulatory therapies not otherwise specified in protocol.
29. The initiation, use or change in the following therapies ≤ 24 weeks prior to Screening, unless a different time frame is indicated:
    a. Use of alkylating agents other than cyclophosphamide (e.g., chlorambucil).
    b. B cell depleting/modulating therapy such as anti-CD20 agents(e.g., belimumab [≤ 16 weeks prior to Screening], atacicept, telitacicept), dual or other anti-B Lymphocyte Stimulator /proliferation-inducing ligand neutralizing therapies (see Appendix 6).
    c. IL-12/IL-23 pathway inhibitors (e.g., ustekinumab).
    d. Anti-IL-6 receptor (tocilizumab, sarilumab) or anti-IL-6 (siltuximab).

e. Anti-IL-1 agents.

f. Type 1 IFN pathways inhibitors (e.g., anifrolumab).

g. JAK-STAT pathway inhibitors (tofacitinib)

Prior/concurrent Clinical Study Experience

30. Treatment with other investigational agents within the last 12 weeks or 5 half-lives or as per washout requirement from the previous protocol, whichever is longest, prior to Screening Visit (e.g., small molecules such as Bruton's tyrosine kinase inhibitors).

Diagnostic Assessments

31. Clinically significant or predefined abnormalities in laboratory tests at Screening Visit:
    - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase > 2.5 × upper limit of normal (ULN);
    - Total bilirubin > 1.5 × ULN;
    - Hemoglobin < 5.0 mmol/L (9 g/dL), white blood cells < 2.5 × 109/L, absolute neutrophil count < 1500/mm^3, or platelets < 75 × 109/L, unless attributable to active SLE;
    - Or thyroid stimulating hormone < 0.01 mIU/L or ≥ 7.1 mIU/L per central laboratory results.
32. Signs of significant chest imaging (chest X-ray, CT, MRI) abnormality (e.g., interstitial lung disease, active TB). Results from a chest imaging study ≤ 3 months of Screening are acceptable if no reason to suspect clinical changes.

Other Exclusions

33. Legal incapacity or limited legal capacity.

5.3 Lifestyle Considerations

Participants are recommended to continue to use sunblock.

5.3.1 Meals and Dietary Restrictions

No food restrictions. On scheduled study visit days with PK assessment (see Table 1), record the date and time of the closest meal before and after the study drug administration.

5.3.2 Activity

Participants will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities (e.g., watching television or reading).

5.4 Screen Failures

Retesting:

During the initial Screening Period or single rescreening period, testing may be repeated once for participants if test results would preclude enrollment in the study and are thought to represent a laboratory error, or a reversible, clinically insignificant intermittent condition, or are inconsistent with the subject's historical values. When a laboratory test needs to be repeated during the Screening Period, or to accommodate other unanticipated events, the Screening Period may be extended to 7 weeks after discussion with the Medical Monitor.

Rescreening:

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once, after approval by the Medical Monitor. Rescreened participants will be assigned a new participant number.

If a participant is rescreened, all Screening tests should be repeated with the exception of:

- Hepatitis and HIV testing must have occurred within 1 month of the initial Rescreening Visit or will need to be repeated during the Rescreening Period.
- Anti-ENA antibodies (anti Sm, RNP, Ro/SSA, La/SSB Abs) must have occurred within 1 month of the initial Rescreening Visit or will need to be repeated during the Rescreening Period.
- Documented TB testing must have occurred within 3 months of the initial Rescreening Visit or need to be repeated during the Rescreening Period.
- Documented chest imaging must have occurred within 3 months of the Rescreening Period otherwise to be repeated during the Rescreening Period.

If inclusion/exclusion criteria are not met based on the results of the repeated testing, the participant should be considered a screen failure and not enrolled in the study. Reasons for screening failure should be recorded in the Case Report Form (CRF).

6 Study Intervention and Concomitant Therapies

Study intervention is any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant per the study protocol.

6.1 Study Intervention Administration

Participants will self-administer study intervention twice per day (every 12 hours ± 2 hours) (See Section 1.3). To maintain blinding, all participants will take 4 tablets in total per dosing (placebo and/or enpatoran tablets, depending on the dose level. Four tablets in the morning and 4 tablets in the evening. See Table 3). On scheduled study visit days, the participant will be asked not to self-administer study intervention at home but to bring the study intervention to the site for administration after the scheduled study visit assessment/procedures are performed (other than post-treatment ECGs and PK/PD sampling). Last study intervention will be administered prior to the EOT visit of the 24-Week DBPC period for those who opt out for the separate LTE study.

Table 3 Study Intervention Administration

Study Intervention Name	Enpatoran	Placebo
Dose Formulation:	Film-coated tablet. All formulation components are of pharmacopoeial grade.	Film-coated tablet. All formulation components are of pharmacopoeial grade.
Unit Dose Strengths/Dosage Levels:	25 mg/ 25 mg, 50 mg, 100 mg	Not applicable.
Route of Administration:	Oral	Oral
Packaging and Labeling:	Film-coated tablets will be packed into Alu/Alu blisters containing 12 units. Each blister will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines.	Film-coated tablets will be packed into Alu/Alu blisters containing 12 units. Each blister will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines.
Dosing Instructions:	- Oral twice per day administration. To be taken with approximately 200 mL water. - No specific food restriction. On scheduled study visit days with PK assessment, record the date and time of the closest meal before and after the study drug administration. **All participants randomized to enpatoran arms:** • For 25 mg dose: 1 × 25 mg enpatoran tablet + 3 × placebo tablets (twice per day) • For 50 mg dose: 2 × 25 mg enpatoran tablets + 2 × placebo tablets (twice per day) • For 100 mg dose: 4 × 25 mg enpatoran tablets (twice per day) **All participants randomized to placebo arm**: • 4 placebo tablets (twice per day)	

6.2 Study Intervention Preparation, Handling, Storage, and Accountability

Enpatoran and placebo will be provided in tablet formulation in an Alu/Alu blister package (see Section 6.1) and it has to be stored at ≤ 30°C (should not be frozen).

Packaging and labeling of enpatoran and placebo tablets will be in accordance with applicable regulatory requirements and applicable Good Manufacturing Practice guidelines. The information on the medication will be in accordance with approved submission documents. Enpatoran and placebo tablets will be packed and labeled to protect the blinded nature of the study. Enpatoran and placebo will not be distinguishable from each other and will be covered by suitable labels to prevent participants and study personnel from noticing any differences in the tablets of enpatoran versus placebo. Blinded treatment kit numbers will be obtained through the Interactive Voice/Web Response System (IVRS/IWRS) as described in Section 6.3.

- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Upon receipt of the study interventions, the Investigator or designee will confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery. Further guidance and information for study intervention accountability are provided in the Study Reference Manual.
- Only participants enrolled in the study may receive study interventions and only authorized site staff may supply it. All study interventions will be stored in a secure, environmentally controlled, and monitored (manual or automated) area, per the labeled storage conditions, and with access limited to the Investigator and authorized site staff.
- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study interventions accountability records at the study site will include the following:
    - Confirmation of receipt, in good condition and in the defined temperature range.
    - The inventory provided for the clinical study.
    - The doses each participant used during the study.
    - The disposition (including return, if applicable) of any unused study interventions.
    - Dates, quantities, batch numbers, blister package numbers, expiry dates of study interventions, and the participant numbers.
- The Investigator site will maintain records, which adequately documents that participants were provided the doses specified in this protocol, and all study interventions provided were fully reconciled.
- Unused study interventions will not be discarded or used for any purpose other than the present study. There will be the option that unused study interventions will be re-dispensed to the same patient controlled by IRT. No study intervention that is dispensed to a participant may be redispensed to a different participant.
- A Study Monitor will periodically collect the study interventions accountability forms.
- Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual.

Participants will record date, time, and amount of study intervention administration in the paper diary card or mobile application provided.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

After confirmation of participant eligibility, study participants in each cohort will be centrally allocated to study intervention using an IVRS/IWRS and per a computer-generated randomization list:

- In Cohort A, the randomization ratio will be 1:1:1:1 ratio (enpatoran 25 mg twice per day: enpatoran 50 mg twice per day: enpatoran 100 mg twice per day: placebo) and the number of study participants randomly assigned to study intervention will be up to 100.
- In Cohort B, the first 60 participants will be assigned with a 2:1 ratio (enpatoran 100 mg twice per day: placebo). And then, participants will be assigned with a 1:1:1:1 ratio (enpatoran 25 mg twice per day: enpatoran 50 mg twice per day: enpatoran 100 mg twice per day: placebo) until the adaptations planned in Cohort B are in place, if any (see Sequence of Analyses). The IVRS/IWRS will be used to assign unique participant numbers, allocate participants to study intervention group at the Randomization Visit in DBPC treatment period, and allocate study intervention to participants at each study intervention visit.

Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information and directions for the IWRS will be provided to each site. The site will contact the IVRS/IWRS prior to starting study intervention administration for each participant.

Participants in Cohort A will be stratified by the following factors:

- Region (3 levels: North America and Western Europe vs Asia vs Central/South America and rest of the world),
- Disease diagnosis at Screening (2 levels: CLE [SCLE and/or DLE] vs SLE).

Participants in Cohort B will be stratified by the following factors:

- Region (3 levels: North America and Western Europe vs Asia vs Central/South America and rest of the world),
- Biomarker status at Screening (2 levels: [IFN-GS high AND/OR positive RNA auto-antibodies: anti-SSA/Ro, SSB/La, Smith/RNP] vs [IFN-GS low AND negative RNA auto-antibodies: anti-SSA/Ro, SSB/La, Smith/RNP]).
- Hybrid SELENA-SLEDAI score at Screening (2 levels: ≥ 10 versus <10).

6.3.2 Blinding

Blinding Method

The study will be double-blind for Cohort A and Cohort B (Parts 1 and 2).

Randomization codes will be kept strictly confidential, accessible only to authorized staff (i.e., randomization statistician, unblinded statistician, IDMC members and statistical data centers, Firewall team, unblinded pharmacist, and the unblinded bioanalytical monitors and laboratories responsible for analyses of the PK), until the time of unblinding. All other study-related individuals, ancillary site staff, clinical research associates/monitors, the Investigator, Sponsor, and clinical research organization staff will remain blinded to study intervention.

The bioanalytical monitors and analytical laboratories responsible for the analysis of the PK samples (requiring shipment of laboratory samples from the site) will be unblinded to study treatment codes to enable sample testing of PK of study intervention prior to database lock. Masked participant identifiers will be used to support association with treatment codes but prevent association of treatment codes with any other clinical data, such as safety and clinical response data.

The EAC will be blinded to treatment. Blinded efficacy and safety data will be provided to the EAC for data monitoring (for more details refer to Appendix 2).

The IDMC and supporting independent statistical data centers will be unblinded to treatment.

In addition, the IDMC will present recommendations based on the results of the interim analyses to the Firewall Team to make final decision (see Section 9.4.4). The Firewall team will be unblinded to treatment and will remain independent from study team. Details will be provided in the Firewall Team charter.

When the study is completed (final analysis for Cohort A and Cohort B), database locked, the data file verified, and protocol violations determined, the drug codes will be broken and made available for data analysis.

Study intervention information that would unblind the study participants will not be reported with participant identifiers to investigative sites or blinded personnel until the study has been unblinded.

Assignment Method Retention

The study blind may be broken in the event emergency unblinding is necessary for participant safety or the reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs).

Unblinding in these cases would be done via the unblinding module in IWRS. All breaks of the study blind must be adequately documented.

6.3.3 Emergency Unblinding

In an emergency, the Investigator is solely responsible for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety is always the first consideration in this decision. If the Investigator decides that unblinding is warranted, the Investigator makes every effort to contact the Sponsor prior to the unblinding, unless this could delay emergency treatment. The Sponsor will be notified within 24 hours after unblinding. The Investigator will provide the Sponsor the reason for unblinding without revealing the study intervention, except to the designated global patient safety representative via the Emergency Unblinding Notification Form. The date of and reason for unblinding will be recorded in the source documents. Contact information for unblinding in an emergency is given on the participant emergency card provided to each participant, as noted in Appendix 2.

The Sponsor's global patient safety department will submit any SUSAR reports to regulatory authorities and ethics committees with unblinded information, per applicable regulations. Only blinded information will be provided to the study team.

Participants undergoing emergency unblinding will be discontinued from the study intervention. The investigations scheduled for the ET and all subsequent Safety Follow-up Visits until EOS should be performed (Section 7.1).

6.4 Study Intervention Compliance

Besides study visits where study intervention will be administered under medical supervision at the site, study participants will self-administer their study intervention at home. They will be provided with a diary card or phone application containing instructions for self-administration and documentation of study intervention intake. If participants use the phone application, they may also receive reminders to administer study intervention and perform related documentation.

When participants self-administer study interventions at home (see Section 1.2), compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned tablets, and review of diary cards or data generated from the phone application using the vendors portal and documented in the source documents and CRF. Any deviation(s) from the prescribed dosage regimen are recorded.

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification may be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

A record of the number of tablets dispensed to and taken by each participant will be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays will also be recorded in the CRF.

6.5 Dose Selection and Modification

- Participants enrolled into Cohort A will be randomized in a 1:1:1:1 ratio receiving placebo or one of the three active doses, i.e. 25, 50 or 100 mg of enpatoran, twice daily while

patients enrolled into Cohort B (SLE) Part 1 will be randomized in a 2:1 ratio receiving either 100 mg enpatoran or placebo twice daily for a treatment duration of at least 24 weeks.

- In Cohort B Part 2, participants will start with a randomization ratio of 1:1:1:1 receiving placebo or one of the three active doses, i.e. 25, 50 or 100 mg of enpatoran, twice per day. Part 2 dose levels and randomization ratio (not exceeding the highest clinically investigated enpatoran dose in the ongoing Phase Ib study: NCT04647708), may be adapted as described in Section 9.4.4.

- Participants from Cohort B will continue on their dose level initiated prior to any potential adaptation until completion of study treatment at Week 24 unless Cohort B is terminated for futility.

6.6 Continued Access to Study Intervention after the End of the Study

Participants who complete the 24-Week DBPC Treatment Period may be offered participation in an optional long-term extension (LTE) study as part of a separate protocol.

6.7 Treatment of Overdose

For this study, any dose of study intervention greater than 300 mg (12 tablets) within 24 hours ± 2 hours or a single dose greater than 200 mg (8 tablets) will be considered an overdose.

The Sponsor has no specific recommendation for treating an overdose. The Investigator will use his/her clinical judgment to manage any overdose, considering the symptoms and any site procedures or standards.

Even if not associated with an AE or a SAE, any overdose is recorded in the CRF and reported to global patient safety in an expedited manner. Overdoses are reported on a SAE and Overdose Report Form, following the procedure in Appendix 4.

6.8 Concomitant Therapy

Record in the CRF all concomitant therapies (e.g., medicines or nondrug interventions, including topical creams and ointments) used from the time the participant signs the informed consent until completion of the study, including any changes. For prescription and over-the-counter medicines, COVID-19 and other vaccines, vitamins, and herbal supplements, record the name, reason for use, dates administered, and dosing information.

Contact the Medical Monitor for any questions on concomitant or prior therapy.

6.8.1 Corticosteroids

Long-term use of CSs should be minimized since its use has been associated with damage, morbidity and mortality in SLE (Doria 2014, Gladman 2003, Ruiz-Irastorza 2012, Thamer 2009, Urowitz 2012). Inhibitors of type I IFN pathway are potentially corticosteroid-sparing by increasing glucocorticoid sensitization (Guiducci 2010, Buckland 2010, Northcott 2021). In order to demonstrate the potential CS-sparing effect of enpatoran and its treatment effect

compared with placebo, it is critical that medical management of these participants must include continuous attempts to taper CS use.

Beginning at Week 2 (~ Day 15) and continuing through Week 12, CS **MUST** be tapered to a prednisone-equivalent dose of ≤ 5 mg/day as clinically tolerated (see protocol-specified CS tapering guidance in Appendix 7).

IMPORTANT: The Investigator must be familiar with and follow the rules for CS dosage during the study (see details of the CS rules and protocol-specified tapering guidance, in Appendix 7). Investigators may adjust the CS dosage of participants, if deemed clinically necessary, in a manner not according to the protocol-specified rules; however, these participants may be considered as non-responder if determined by the Endpoint Adjudication Committee (EAC) (see Table 8). Classification as non-responder has no impact on study procedures. Participants adjudicated as non-responders by the EAC may continue on study treatment until Week 24 of the DBPC period, followed by the Safety Follow-Up period.

6.8.2 Corticosteroids Rescue Medication

The following CS rescue rules will apply during the 24-Week DBPC period for participants in Cohort A or Cohort B:

Control of disease activity/flare with a brief steroid rescue is allowed only once after Day 1 through Week 8. During this period, participants may increase the CS dose up to 30 mg/day prednisone-equivalent as rescue for worsening of SLE or CLE activity but must be tapered within 7 days to ≤ CS dose used before the rescue (if not on any CS before the rescue, tapering within 7 days to 5 mg/day is allowed).

Any CS increase after Week 8 for the treatment of worsening CLE or SLE indicates non-responder status. Participants with CS increase for reasons other than treatment of worsening CLE or SLE (e.g., infection, concomitant medical condition) may be classified as non-responders if determined by the EAC. Classification as non-responder has no impact on study procedures. The non-responders will continue on study treatment unless meeting criteria for treatment discontinuation (see Section 6.8).

The EAC has the final decision for non-responder classification related to use of prohibited medications.

6.8.3 Permitted Medicines

All background therapy for SLE and CLE given prior to Screening must be stable or discontinued according to the specifications in the exclusion criteria for a participant to be eligible for the study (see Section 5.2 for Screening Period and Appendix 6 for additional details on SLE/CLE background therapy). As changes in standard SLE or CLE therapy can affect disease activity and PD endpoints, confounding the study findings, all background antimalarial and immunosuppressant therapies should remain stable during the Screening and 24-Week DBPC

Periods. In addition, medication should NOT be adjusted or discontinued prior to Screening in order to allow the participant to become eligible.

The only permitted medications are the following:

1. Any medications required per the medical history and not specifically prohibited by the protocol during the study (i.e., from Screening Visit to the End of the study).
2. COVID-19 vaccines. See Section 2.3.3.
3. Vaccination for influenza virus and S. pneumoniae is allowed during Screening providing that vaccination completes 2 weeks before the Day 1 Visit.
4. Corticosteroid dose up to daily equivalent of prednisone 30 mg maximum for SLE and CLE participants (see Appendix 7). Inhaled CS (asthma, COPD) with requirement for stable dose during the study.
5. Topical corticosteroids: Class I, II or III in stable application for ≤ 4 weeks, up to 2 times per day.
6. Topical calcineurin inhibitors in stable application up to 1 time per day. Oral tacrolimus up to 0.1 mg/kg.
7. Use of 1 antimalarial such as hydroxychloroquine (up to 400 mg/day) or chloroquine (up to 500 mg/day) is permitted; doses should remain stable. For any changes in doses, the Medical Monitor should be contacted, and then the changes should be carefully noted.
8. Permitted SoC therapy during the study for SLE and CLE including the use of 1 of the following single immunosuppressants or immunomodulators (see Appendix 6 for maximum permitted doses in each case):

    - Azathioprine
    - 6-mercaptopurine
    - Mycophenolate (either as mycophenolate mofetil or mycophenolate sodium)
    - Methotrexate
    - Sulfasalazine
    - Leflunomide
    - Dapsone
    - Retinoids

    Note: these medications must be stable throughout the 24-Week DBPC period periods in addition to the Screening Period, see Section 5.2.

    Although it is expected participants will be on SoC medications, not all therapies are permitted, as detailed in Section 6.8.4.

9. NSAID may be used as needed for temporary relief of symptoms. Any changes in NSAIDs up to 1 day prior to each study visit that could affect assessments (e.g., pain) should be avoided.

10. Vitamin D and calcium supplementation are encouraged per local SoC guidelines. Participants not already taking these medications at Screening should, according to the Investigator's judgment, initiate treatment as soon as possible after Screening. These medications will not be supplied by the Sponsor.

11. Low-dose aspirin (≤ 350 mg/day) for cardiovascular prophylaxis or other indications.

12. Stable dose and regimen of anticoagulants.

13. Treatment with a stable dose of over-the-counter supplements (nonherbal [e.g., iron supplement] is allowed if initiated before the Screening Visit). See Section 6.8.3 and Appendix 6 for prohibited supplements.

14. Paracetamol (acetaminophen) up to 3 g/day may be initiated or continued for pain control of SLE symptoms during the study. This should be titrated off as tolerated.

15. Opioids are permitted for stable use for SLE if initiated by Day 1. Initiation of opioids and/or as needed dosing of opioids for more than 2 weeks after Day 1 for SLE is not permitted. These may be titrated off as tolerated during the study.

16. Analgesics may be used at stable doses or as needed basis for temporary relief of symptoms not due to SLE. Any changes in analgesics up to 1 day prior to each study visit that could affect the assessments (e.g., pain) should be avoided (see Section 6.8.4 and Appendix 6 for prohibited medicines).

17. It is recommended that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers if used at Screening be maintained at a stable dose during the study for safety reasons (e.g. hypertension, cardiac failure etc.). Participants with certain degrees of lupus nephritis (≤ 4 mg/mg by spot UPCR) will be permitted into the study and the proteinuria will be followed, unless dose change, or initiation is required for safety reasons.

18. Medications for the treatment of infections and hypersensitivity reactions will be provided at the discretion of the Investigator. If systemic CS are deemed necessary, their use should follow the guidelines in Appendix 7, unless deviation from these guidelines are deemed medically necessary.

19. Any medicines that are considered necessary to protect the participant’s welfare in emergencies may be given at the Investigator’s discretion, regardless if it results in a protocol deviation and the Medical Monitor must be informed.

20. Sunscreen

6.8.4 Prohibited Medicines

The following types of medication are not permitted during the study; see Appendix 6 for further details on medication guidance and specific prohibited medications:

1. Immunomodulator or immunosuppressant therapies not listed in Section 6.8.3.
2. Use of more than 1 medication considered to have immunosuppressant or immunomodulatory properties, not including antimalarials or CS.
3. Use of more than 1 antimalarial therapy.
4. Medications associated with serotonin syndrome.
5. Use of medications associated with AOX inhibition (see Table 6).
6. Biologic therapies for SLE or CLE. Biologic therapies for other indications must be discussed with the Medical Monitor with the exception of insulin or denosumab, which are permitted.
7. Vaccines.
    a. COVID-19 vaccines unauthorized and not approved by the country-specific health agencies or a live or live attenuated virus vaccine. See Section 2.3.3.
8. Supplements (herbal/nonherbal/Chinese Medication). Treatment with a stable dose of over-the-counter supplements (nonherbal) is allowed if nonherbal supplements are initiated before the Screening Visit (except for those stated in Appendix 6).
9. Corticosteroids > 30 mg daily prednisone-equivalent for SLE and CLE. See Appendix 7 for additional CS rules.
10. Topical corticosteroids Class I, II or III applicated for > 4 weeks, or > 2 times per day. Topical corticosteroids Class IV are not allowed.
11. Topical calcineurin inhibitors applicated > 1 time per day. Initiation of, or change in, dosing of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker.
12. Initiation or change in dose of anticoagulation or antiplatelet therapy.
13. Nonsteroidal anti-inflammatory drugs used above maximum prescribed dose per local label.
14. Other investigational agents not specified in this study.
15. Change in dosing or discontinuation of leflunomide less than 8 weeks prior to Screening.

Any medication administered during the study and related to an increase in CLE disease activity should be discontinued (e.g., protein pump inhibitors, terbinafine).

Temporary suspension of QT prolonging medications for the duration of the study should be considered at the Investigator's discretion.

Any additional concomitant therapy that becomes necessary during the study and any change to concomitant therapies must be recorded in the corresponding section of the CRF, noting the name, dose, duration, and indication of each drug.

The SoC medications are part of the participant's SLE and CLE treatment prescribed by the treating clinician and will not be provided by the Sponsor.

The EAC has the final decision for treatment failure (i.e., non-responder) classification.

Refer to the exclusion criteria (Section 5.2) for prohibited medication uses before study enrollment.

6.8.5 Other Interventions

Use of potentially excluded procedures such as acupuncture or joint replacement therapy is to be discussed with the Sponsor or designee on a case-by-case basis. Use of acupuncture is allowed to continue if it is started before the Screening Visit. Major elective surgeries such as abdominal, thoracic or joint replacement surgeries should not be planned to occur in the Study Period. Unplanned joint replacement surgery should be discussed at the earliest opportunity prior to the surgery with the Medical Monitor regarding continuation of the participant in the study.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

7.1.1 Temporary Discontinuation

Study intervention may be stopped at any time at the Investigator's discretion; however, the Medical Monitor must be notified if the participant has missed doses of study intervention for at least 5 consecutive days. The participant will continue their scheduled visits. If the participant's temporary discontinuation is due to an AE, see Section 8. Consultation with the Medical Monitor prior to restarting study medication is advised.

If the participant is unable to resume study intervention, see Section 7.1.2.

7.1.2 Permanent Discontinuation

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant is encouraged to remain in the study until last safety follow-up (i.e., Week 26). The participant should complete the ET assessments as soon as possible and revert to the same study schedule (Table 1) based on the participant's Day 1 until the Safety follow-up visits are completed (see Section 1.3).

The participant must be withdrawn from study intervention in the event of any of the following:

- Enrollment despite violation of an exclusion criterion which, in the Investigator's and/or Sponsor's opinion, makes discontinuation of the participant necessary.
- Participation in any other interventional study during the duration of this study for which the Investigator considers discontinuation of the study intervention necessary.
- Occurrence of pregnancy.
- Occurrence of a clinical condition (e.g., SAE, SFI defined severe flare) for which discontinuation is considered necessary by the Investigator and/or the Sponsor/designee.
- Occurrence of CNS related AE, i.e. seizure, suicide attempt or ideation, which is assessed to be related to the study intervention.
- Non-compliance to study visits, study intervention etc., judged as significant by the Investigator or Sponsor, e.g., taking < 80% of the study intervention doses.
- An unplanned event that necessitates discontinuation of study intervention for more than 4 weeks.
- If a participant is unblinded.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may discontinue from the study at any time, at [his/her] own request or at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- A participant is considered discontinued from the study due to death.
- A participant must be discontinued from the study in the event the participant is lost to follow-up.
- At the time of discontinuing from the study, if possible, a discontinuation visit (i.e., early termination visit) will be conducted, as listed in the SoA. The SoA specifies the data to collect at early termination and safety follow-up visits, and any additional evaluations that need to be completed.
- If the participant revokes consent for the study, any data collected up to that point may still be used, but no future data can be generated, and any biological samples collected will be destroyed.
- A participant has the right at any time to request destruction of any biological samples taken. The Investigator will document this in the site study records and the CRF and inform the Sponsor. The samples will be destroyed.

When a participant must be withdrawn from the study, the Investigator or designee will inform the Medical Monitor immediately, who will then inform the Sponsor's medically responsible individual (or Medical Responsible).

7.3 Lost to Follow-Up

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

The following actions will be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wants to or should continue in the study.
- Before a participant is deemed "lost to follow-up", the Investigator or designee will make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant's last known mailing address, and 3) if a participant has given the appropriate consent, contact the participant's general practitioner or caretaker (where allowed by local regulations) for information. These contact attempts will be documented in the participant's medical record.
- If the participant continues to be unreachable, he/she will be deemed as "lost to follow-up".

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the SoA.
- No protocol waivers or exemptions are allowed.
- Immediate safety concerns are discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations will be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened, to confirm eligibility, and if applicable, record reasons for screening failure.
- Prior to performing any study assessments that are not part of the participant's routine medical care, the Investigator will obtain written informed consent as specified in Appendix 2.
- Procedures conducted as part of the participant's routine medical care (e.g., blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Laboratory results that could potentially unblind the study such as C3, C4, anti-dsDNA, and immune cell subset counts by flow cytometry will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

- For study visits where several assessment procedures coincide, vital signs and PROs should first be assessed, then ECG, collection of urine and blood including PK/PD sampling at their specified times, followed by physician assessments, and any remaining procedures. Vital signs and ECG should be performed after at least 5 minutes of rest.
- Flare history in the 12 months prior to Screening should be collected as described in Section 8.2.5.
- No more than 75 mL of blood may be drawn in a 24-hour period, and no more than 150 mL of blood in a 4-Week period.
- Where allowed by local law/regulations, samples collected during this clinical study may be transferred to a biobank and used for future research outside the clinical protocol when additional consent for this purpose is given. Transfer to the biobank will be documented and any testing of coded biobank samples will **not** be reported in the clinical study report (CSR).
- The long-term storage of samples after study completion for future research may be performed with all sample types collected in the study (e.g., PK, pharmacogenetics, biomarkers) if the participant consents to optional future medical research.

8.1 Efficacy Assessments and Procedures

Efficacy will be assessed using the instruments and outcomes described below and at the visits specified in Table 1.

- Efficacy assessments: CLASI, BILAG 2004, hybrid SELENA-SLEDAI, SFI, 28-joint count, Cutaneous Lupus Activity Investigator's Global Assessment (CLA-IGA), Physician's Global Assessment for SLE Disease Activity, Physician's Global Assessment of Cutaneous Lupus Disease Activity, and MoCA test.
- Patient-Reported assessments: FACIT-fatigue, MOS Sleep Tests, Lupus Symptom Severity Diary (Lupus SSD), PROMIS Physical Function 10a, Patient Global Assessment of Lupus Symptom Severity (PtGA), Patient Global Impression of Change in Lupus Symptom Severity (PGIC), Patient Global Assessment of Lupus Skin Symptom Severity (Skin PtGA), Patient Global Impression of Change in Lupus Skin Symptom Severity (Skin PGIC), Skindex 29 + 3, and Itch NRS. Patient-reported assessments that do not directly support the secondary endpoints may only be implemented if, and when translations are available for use.
- Skin photography. Depending on the site of the lesion, images will be collected with standardized photography equipment for the target lesion (close-up and global), and any other lesions located in the head, face, upper anterior or upper posterior. During the Screening visit, collection of these images is required to confirm SCLE and/or DLE diagnosis for CLE participants with only historical skin biopsy or if collection of skin biopsy is unsuitable (e.g., malar rash bridge of the nose, scalp) and is optional for CLE participants with fresh skin biopsy. Starting at Day 1, optional skin photography will be done in Cohort A participants at selected sites only, which may be used in exploratory analyses to evaluate association of images with other measures of CLE activity, such as

CLASI data. The follow-up photographs should re-evaluate the same area of active disease as originally assessed at Day 1. Images will be graphically masked by placing black boxes over eyes, tattoos, identifiable features to 'deidentify' images. Further information is provided in the user manual.

- Other patient experience assessments: In-trial qualitative interview.

Details related to efficacy assessments and procedures are summarized in Appendix 8.

Data collection and all query handling will be done via an eCRF system. An electronic device (electronic PRO [ePRO] system) may be used to collect some of the patient-reported assessments.

8.2 Safety Assessments and Procedures

The safety profile of the study intervention will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings, vital signs, electrocardiograms, occurrence of suicidal behavior and ideation, and laboratory tests.

Comprehensive assessment of any potential toxicity experienced by each participant will be conducted starting when the participants give informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant; the reporting period is specified in Section 8.3.

8.2.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the skin, ENT, cardiovascular, respiratory, gastrointestinal, and musculoskeletal systems.
- Routine neurological examination, which includes but not limited to assessment of mental status, cranial nerves, reflexes, motor-sensory system, and gait-coordination.
- The information obtained by physical examinations will complete SLE and CLE disease activity assessments.
- Additional examination may be performed at the discretion of the Investigator to fully evaluate participant's complaints or AEs.
- Investigators will pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

- Blood pressure and participant's position; pulse; respiratory rate; temperature and location of measurement, weight, and height (at Screening only) will be measured and recorded. Body mass index will be calculated at Screening only.
- Blood pressure and pulse measurements will be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones) and measured with an automated device. Manual techniques will be used only if an automated device is not available.

8.2.3 Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically measures heart rate, PR, RR, QRS, QT, and QTcF (Fridericia's formula [QTcF]). Twelve-lead ECG recordings will be obtained after approximately 5 minutes rest in a supine position.
- The parameters and overall evaluation (normal/abnormal) will be recorded in the eCRF. Abnormal values judged as clinically significant by the Investigator will be documented on the AE page (see Section 8.3.8).
- The printout of the ECG is to be signed, dated, and filed in the Investigator's study file along with a signed and dated copy (if the printouts are not on archive-quality paper). In addition, ECGs will also be stored digitally by the Sponsor.

8.2.4 Clinical Safety Laboratory Assessments

- Blood and urine samples will be collected for the clinical laboratory tests listed in Appendix 5 at the time points listed in the SoA. All samples will be clearly identified and detailed in the Laboratory Manual. No fasting is required for laboratory tests.
- Repeat tests may be performed at any time during the study, as determined necessary by the Investigator or required by local regulations.
- The tests will be performed by a central laboratory with the exception of urinalysis and microscopy, urine pregnancy tests, ESR, T-SPOT TB test (if required, see Section 5.2), SARS-CoV-2 test if required, and any applicable vaccines which will be performed by a local laboratory or locally.
- Local laboratory results are only required when central laboratory results are not available in time for study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make a study intervention decision or response evaluation, the results will be recorded.
- The Sponsor will receive a list of the local laboratory normal ranges before shipment of study intervention(s). Any changes to the ranges during the study will be forwarded to the Sponsor or designated organization.
- The following safety laboratory assessments will be performed at Screening only:
    - Follicle stimulating hormone (FSH) and estradiol (for women of nonchildbearing potential only to determine postmenopausal status).
    - Serum pregnancy test (for women of childbearing potential only).
    - Serum virology (Exclusion Criterion 12, Section 5.2), except for reflex testing of HBV DNA is required.
    - Thyroid stimulating hormone (TSH)
- Pregnancy testing (serum or highly sensitive urine, as required by local regulations) will be conducted at monthly intervals during study intervention administration.

- Pregnancy testing (serum or highly sensitive urine, as required by local regulations) will be conducted at the end of relevant systemic exposure of the study intervention and correspond with the time frame for female participant contraception in Section 5.1.
- Additional serum or urine pregnancy testing may be conducted at any time during the study to establish the absence of pregnancy, at the Investigator's discretion or if local regulations require them.
- Amylase and lipase will be tested at Screening and Day 1 but may be assessed as clinically indicated (per Investigator's judgment). Reflex amylase isoenzymes will be tested only when total amylase levels are elevated.
- The Investigator will review each laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE, unless it does not meet the AE definition, as specified in Appendix 4. The laboratory reports will be filed with the source documents.
- Methods for sample identification during shipping and handling, as well as sampling methods, processing, and storage of samples are detailed in the Laboratory Manual.

8.2.5 Disease and Disease Treatment History

Disease history and details of prior treatment for disease must be collected at Screening, as described below.

For SLE, disease history, including and not limited to flare history, in the 12 months prior to Screening must be collected. A flare is a measurable increase in disease activity in 1 or more organ systems involving new or worse clinical signs and symptoms and/or laboratory measurements. It must be deemed clinically significant by the assessor and usually there would be at least consideration of a change or an increase in treatment (Ruperto 2011). Examples of severe flares could include new or worsening organ threatening disease, and hospitalization. Current documentation of ACR/SLICC/EULAR/ACR 2019 classification criteria will be collected and recorded in the CRF. All previous SLE manifestations should be collected on the Medical History page of the CRF.

For CLE subtypes, predominant findings of lupus rash must be SCLE and/or DLE based on clinical and histopathology (historical dermatopathology report or fresh skin biopsy) findings and supported by laboratory results. If only historical dermatopathology report is available, diagnosis must be confirmed by skin photography at Screening visit. Participants with cutaneous lupus lesions unsuitable for biopsy (e.g., malar rash, bridge of the nose, or scalp) may be evaluated by skin photography at Screening visit, on a case-by-case basis. Disease history including flare history and mucocutaneous and scalp involvement in the 12 months prior to Screening must be collected. A flare is a measurable increase in skin activity, which is deemed clinically significant by the assessor and usually accompanied by a change or an increase in treatment. Documentation of SCLE and/or DLE clinicopathologic criteria (and CLE subtypes) will be collected and recorded in the CRF based on the modified Gilliam criteria (Werth 2020). Additional features of acute cutaneous lupus or tumidus lupus will not exclude the participant as long as the predominant features support a lead diagnosis as SCLE and/or DLE. All previous

CLE manifestations and CLE subtypes should be collected on the Medical History page of the CRF.

Medication history – Treatment of SLE and CLE in the 12 months prior to Screening must be recorded in the CRF. In addition, all previous SLE and CLE medications, other medications including investigational drugs up to 12 months prior to Screening must be recorded on the previous treatment page of the CRF.

8.2.6 Suicidal Ideation and Behavior Risk Monitoring

Nonclinical studies found that M5049 crosses the blood brain barrier. In addition, because people with SLE and CLE are more prone to depression, the Sponsor will closely monitor for any CNS and mental status changes during the course of the study.

Due to disease-related propensity to neuropsychiatric conditions (e.g. depression change in mood/ behavior) in the disease population and nonclinical study finding demonstrating enpatoran potential to penetrate BBB.

- All study participants will be monitored appropriately and observed closely for suicidal ideation and behavior change throughout the study, especially at the beginning and end of the intervention, or at the time of dose changes. The Investigator will consider discontinuing the study intervention in participants, who experience signs of suicidal ideation or behavior, following a risk assessment.
- When informed consent or assent has been given, participants will be instructed to alert family members to watch for the emergence of unusual changes in mood, behavior, as well as the emergence of suicidal ideation or attempts and to report such symptoms immediately to the Investigator.
- The C-SSRS (Appendix 8) will be used for assessment of suicidal ideation and behavior change at the baseline and during the study. Notable changes in the behavior or indication of suicide (ideation or attempt) that are documented on the questionnaires anytime during the study should be reported as clinical AEs. Consider discontinuing the study intervention in participants, who experience signs of suicidal ideation or behavior, following a risk assessment.

8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting

- The definitions of an AE and a SAE are in Appendix 4.
- The Investigator and any qualified designees (e.g., Sub-Investigators) are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. The Investigator remains responsible for following up AEs that are serious or that caused the participant to discontinue the study intervention, as specified in Section 8.3.2.
- Requests for follow-up will usually be made via the Sponsor or CRO-designated study team member, although in exceptional circumstances the global patient safety department may contact the Investigator directly to obtain further information or to discuss the event.

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are in Appendix 4.
- All AEs and SAEs will be collected from the signing of the ICF until final safety follow-up visit at the time points specified in the SoA (Section 1.3). Beyond this reporting period, any new unsolicited SAEs that the Investigator spontaneously reports to the Sponsor will be collected and processed.
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance will this exceed 24 hours, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available using the same procedure that was used for the initial report.
- Investigators are not obligated to actively solicit information on AEs or SAEs after the end of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator will promptly notify the Sponsor.

8.3.1 Method of Detecting Adverse Events and Serious Adverse Events

At each study visit, the participant will be queried on changes in his or her condition.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are in Appendix 4.

8.3.2 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AESIs (as defined in Section 8.3.7), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Reasonable attempts to obtain this information will be made and documented. It is also the Investigator's responsibility to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. Further information on follow-up procedures is in Appendix 4.

8.3.3 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of an SAE (particularly life-threatening and deaths) is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The

Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

Individual Case Safety Reports will be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators, as necessary.

An Investigator who receives an Individual Case Safety Report describing a SUSAR or other specific safety information (e.g., Emerging Safety Issue Report, summary or listing of SAEs/SUSARs) from the Sponsor will review and file it in the Investigator's Site File and will notify the IRB/IEC, if appropriate according to local requirements.

In this global clinical multicenter study, the Sponsor is in the best position to determine an unanticipated problem (as defined in US Regulations 21 CFR 312.66). The Sponsor will immediately notify all Investigators of findings that could adversely affect the safety of participants, impact the conduct of the study or alter the IRB's approval/favorable opinion to continue the study. An unanticipated problem is a serious AE that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report, specified in Section 2.3.

8.3.4 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until 90 days post-intervention contraception described in Section 5.1 and Table 4.
- If a pregnancy is reported, the Investigator will record the pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. Adverse pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered and reported as SAEs. A spontaneous abortion (occurring at <22 weeks gestational age) or stillbirth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- The participant /pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant /pregnant female partner and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date for a healthy newborn. In case of a congenital anomaly or other illness of the newborn, follow-up will continue until the illness has resolved or there is a definite outcome of the event.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as specified in Section 8.3.3. While the Investigator is not obligated to actively seek this information in former study participants pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.
- Prior to continuation of study intervention following pregnancy, the following will occur:
  - The Sponsor and the relevant IRB/IEC give written approval
  - The participant gives signed informed consent
  - The Investigator agrees to monitor the outcome of the pregnancy and the status of the participant and her offspring.

8.3.5 Cardiovascular and Death Events

Not applicable.

8.3.6 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.3.7 Adverse Events of Special Interest (AESI)

An AESI (a serious or non-serious AEs deemed related to the study intervention) is one of the scientific and medical concern specific to the study intervention i.e. enpatoran, for which ongoing monitoring and prompt communication by the study Investigator to the sponsor is required. Such AEs of interest may warrant further investigations and in-depth evaluation to better characterize and understand the association between the AE and study intervention. Based on the enpatoran mode of action and findings of nonclinical toxicology studies, the following clinical experiences are considered as AESIs:

- Severe infections CTCAE grade ≥ 3
- Seizure (any CTCAE grade)
- Clinically significant cardiac arrythmia
- Serotonin Syndrome

Upon observation of AE that qualifies to be an AESI, the Investigator must complete an AESI report Form and communicate the event/s with the sponsor within 24 hours of occurrence of any AESI. AESI classified as serious based on SAE reporting criteria should always be reported as SAE as outlined in Section 8.3.3.

8.3.8 Management of Adverse Events (Including AESI)

Standard medical care will be provided at the study site for all AEs occurring during the study in accordance to the institutional guidelines. The severity of AEs will be graded per National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE,

Version 5.0). The reason for study intervention withdrawal and the nature, duration, and results of any follow-up observations should be recorded in the appropriate section of the eCRF.

The study intervention may be interrupted at any time at the Investigator's discretion; however, the Medical Monitor must be notified. Re-initiation of study intervention may occur at the discretion of the Investigator with consideration of the following:

Clinical signs and symptoms	**Proposed actions**
Cardiac Signs and symptoms (e.g., palpitation, presyncope/syncope, dizziness)	• Temporarily withhold study intervention • Perform clinical evaluation including physical examination (PE), ECG, Vitals, blood pressure • Review of concomitant medication • Withhold offending medications if appropriate • If toxicity of CTCAE Grade ≥ 3 persists and /or alternative cause unclear; may discontinue study intervention permanently
Neuropsychiatric signs & symptoms (e.g., severe & unremitting headache, new onset seizure; signs of depression; suicidal ideation / tendency and sign and symptoms consistent with serotonin syndrome)	• Temporarily withhold study intervention. • Clinical & diagnostic evaluation including complete neurological assessment, diagnostic test (as needed) should be performed. • Review of concomitant medication; suspend any offending medication as appropriate • Permanently discontinue study intervention if meets Hunter serotonin toxicity criteria and/ or a new onset seizure or suicide ideation / attempt should be reported within 24 hours of awareness.
Severe Infections Grade ≥ 3	• If severe infection (CTCAE Grade ≥ 3), study intervention should be withheld until recovery. • Signs & symptoms should be managed in accordance to the institutional guidelines. • Re-initiation of the study intervention should be discussed with Medical responsible • Permanently discontinue study intervention if severe infection is CTCAE Grade ≥ 4.

Asymptomatic Abnormal Laboratory Values	**Proposed Actions**
Neutrophil count: <1,000/mm³ [Grade ≥ 3]	• Temporarily withhold the study intervention. • Clinical evaluation per institutional guidelines. • Repeat the test, preferably within 72 hours but no later than 7 days. • Withhold offending concomitant medication, if appropriate. • Determine alternative contributing factors • If retest confirms the Grade ≥ 3 toxicity & alternative etiology [confounding factors such as concurrent medications or disease, disease flare or other risk factors] is not confirmed, permanently discontinue the study intervention. • Monitor until resolution or return to baseline, non-clinically significant level.
Platelet count: <50,000/mm³ [Grade ≥ 3]	
Lymphocyte count: <500/mm³ [Grade ≥ 3]	
Transaminase elevation i.e. ALT and /or AST > 3xULN (if baseline is normal) or > 3 × baseline (if baseline is abnormal) [Grade ≥ 2]	
Isolated elevation of Total Bilirubin i.e., > 2 × ULN (unaccompanied by transaminase elevation)	
eGFR < 40 mL/min/1.73m²	

The eGFR is calculated by the Modification of Diet in Renal Disease equation: eGFR = 175 × (serum creatinine in mg/dL)$^{-1.154}$ × (age in years)$^{-0.203}$ × 0.742 (if female) × 1.212 (if race is black).	• Study intervention may be re-initiated if retest value returns to baseline or not clinically significant value after discussion with Medical responsible.
Serum creatinine > 3.0 × Baseline (Grade ≥ 3)	

8.4 Pharmacokinetics

- The following PK parameters will be calculated, when appropriate:

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

- Whole blood samples of approximately 3 mL will be collected for measurement of plasma concentrations of enpatoran. Collection times are specified in the SoA (Section 1.3). The actual date and time (24-hour clock time) of each sample will be recorded to calculate actual time elapsed since the prior dose administration. The sampling timing may be altered during the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The exact date/time of sample collection and study intervention administration must be recorded in the CRF and will be used in the calculation of PK parameters. Time deviations from planned PK sampling times will not be considered a protocol deviation provided the exact date/time of sample collection and study intervention administration are recorded in the CRF. The time at which the closest meal was consumed should also be recorded on the CRF on scheduled study visit days with PK assessment.
- The acceptable PK time windows for the respective scheduled days and time points of the nominal postdose sampling times (see Section 1.3) are:
    - Between 1 hour and 2 hour postdose samples
    - Between 4 hour and 6 hour postdose samples
    - Week 16, Week 20, and Week 24:
      Blood collected any time of the visit. Record time of previous dosing and PK sampling time.
- The quantification of enpatoran in plasma will be performed using a validated liquid chromatography-mass spectrometry assay method. Concentrations will be used to evaluate the PK of enpatoran.
- Remaining samples collected for analyses of enpatoran concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Details on processes for collection and handling of these samples are in the Laboratory Manual. Retention time and possible analyses of samples after the End of Study are specified in the respective ICF.

- All blood samples collected for PK analysis (except those from placebo dosed participants), as detailed in the SoA, that are within the known stability of enpatoran at the time of receipt by the bioanalytical laboratory, may be analyzed.
- Plasma concentrations (and PK parameters using noncompartmental methods, as appropriate) will be listed and summarized by study day (and time window, as appropriate) and dose group.

Further exploratory PK analysis may be performed using noncompartmental methods and/or population PK modeling, as appropriate (see details of PK analyses in Section 9.4.3.1).

8.5 Pharmacogenetics

- Samples are collected only where allowed by local law/regulations. Where local regulations and IRB/IEC allow, a blood sample of approximately 6 mL will be collected for DNA analysis from consenting participants. Collection time is specified in the SoA.
- Participation in pharmacogenetic research is optional. Participants who do not wish to participate in the pharmacogenetic research may still participate in the study. An exploratory evaluation of correlations between DNA germline polymorphisms and PK, study intervention benefit, and AEs may be conducted and documented.
- In the event of DNA extraction failure, a replacement sample for pharmacogenomics testing may be requested from the participant. Additional informed consent will not be required to obtain a replacement sample.
- Appendix 9 provides further information on pharmacogenetics research.

8.6 Biomarkers

Collection of biological samples for other biomarker research is also part of this study; they are collected only where allowed by local law/regulations. The following samples for biomarker research will be collected from all participants in this study (except the Skin biopsy which is optional) as specified in the SoA (Section 1.3).

- Blood samples of approximately 13 mL will be tested for SLE disease activity markers (Anti-dsDNA antibodies; Complement C3, C4), immunoglobulins (IgG, IgA, IgM), antiphospholipid Abs (Anti-cardiolipin IgG, IgM; anti-β2 glycoprotein IgG, IgM; Lupus anticoagulant; dRVVT or other), and anti-ENA Abs (anti Sm, RNP, Ro/SSA, La/SSB) to evaluate the PD effect of enpatoran.
- Blood samples of approximately 9 mL will be tested for levels of serum biomarkers (e.g., cytokines) to evaluate the PD effect of enpatoran compared to placebo.
- Blood samples of approximately 2 mL will be tested for levels of IFN-GS for the purposes of patient stratification.
- Blood samples of approximately 5 mL will be tested for levels of gene expression (RNA) to evaluate the PD effect of enpatoran compared to placebo.
- Blood samples of approximately 5 mL will be tested for levels of immune cell subsets to evaluate the PD effect of enpatoran compared to placebo.

Samples will be tested with an assay with an appropriate regulatory status by a certified laboratory in accordance with relevant GCP and applicable local, state and/or national regulations. The use of testing results for patient stratification in this study is considered investigational.

Skin biopsies (one pre-treatment and one on-treatment preferably on the same target lesion, both optional [if timing for on-treatment biopsy had to be adjusted, prior discussion with medical monitor is needed]; punch biopsy) will be evaluated for various biomarkers (e.g., gene expression [e.g., IFN-GS], immunohistochemistry [e.g., MxA expression)]. If local regulations allow, samples collected during this clinical study may be transferred to a biobank and used for future research outside the clinical protocol when additional consent for this purpose is given. Transfer to the biobank will be documented and any testing of coded biobank samples will not be reported in the CSR.

In addition, participant samples may be used for additional research, as specified in the ICF.

Details on processes for collection and handling of these samples are in the Laboratory Manual. The Sponsor will store the samples in a secure storage space with adequate measures to protect confidentiality. Retention time and possible analyses of samples after the End of Study are specified in the respective ICF.

8.7 Immunogenicity Assessments

Not applicable.

8.8 Health Economics

Not applicable.

9 Statistical Considerations

9.1 Statistical Hypotheses

Each cohort has its own primary objective and the respective null hypothesis will be tested with a 1-sided alpha of 2.5% separately.

Participants with CLE (active SCLE and/or DLE) or SLE with predominantly active rash (Cohort A)

The global null hypothesis for the Cohort A primary objective is the hypothesis that there is no dose-effect, which can also be stated as the hypothesis that the primary endpoint means across the study arms are equal.

The global null hypothesis is:

- H0: $\mu(1) = \mu(2) = \mu(3) = \mu(4)$ Hypothesis of no difference between study arms

  with $\mu(k)$ standing for the mean percent change from baseline of CLASI-A at Week 16 in the study arm k, k =1 to 4, with: 1 = Placebo only, 2 = enpatoran 25 mg twice per day, 3 = enpatoran 50 mg twice per day and 4 = enpatoran 100 mg twice per day. And μ is the vector of $\mu(k)$, k =1 to 4.

H0 is tested against the alternative hypothesis (H1) is that at least one of μ(2), μ(3) and μ(4) is < μ(1).

The global null hypothesis can be rejected, if at least one of the following contrast test can be rejected. An optimal contrast is defined for each candidate model M(m), m =1 to 5 as detailed in Section 8.2, is c(m)'. For each candidate model, the null hypothesis H0(m): c(m)' μ = 0 is tested against H0(m): c(m)' μ < 0.

The model M that fits the data best (e.g. smallest AIC statistic) will be chosen for dose-estimation and to further compare each enpatoran study arm to placebo: for each k=2 to 4, the null hypothesis H0'(M, k): μ(1) = μ(k) will tested versus H1'(M, k): μ(k)< μ(1k)

Participants with active SLE (Cohort B)

The global null hypothesis for the Cohort B primary objective is the hypothesis that there is no dose-effect, which can also be stated as the hypothesis that the primary endpoint means across the study arms are equal.

The global null hypothesis is:

H0: μ(1) = μ(2) = μ(3) = μ(4) Hypothesis of no difference between study arms

with μ(k) standing for BICLA response rate at Week 24 in the study arm k, k = 1 to 4, with: 1 = Placebo only, 2 = enpatoran 25 mg twice per day, 3 = enpatoran 50 mg twice per day and 4 = enpatoran 100 mg twice per day. And μ is the vector of μ(k), k=1 to 4.

H0 is tested against the alternative hypothesis (H1) is that at least one of μ(2), μ(3) and μ(4) is > μ(1).

This global null hypothesis will be tested in a two-stage adaptive design where stage-wise test statistics are combined using a weighted inverse normal method (Lehmacher 1999). In Stage 1, participants are only assigned to study arm 1 and 4 but not 2 and 3. The following potential adaptations after Stage 1 are planned: extension of investigated study arms (i.e. assigning participants also to study arm 2 and 3) or stop for futility. Rejection of H0 is only possible after stage 2 if $w_1Z_1 + w_2Z_2 > z(\alpha)$ where $z(\alpha)$ is the upper tail of the standard normal distribution and w_1, w_2 are pre-specified weights and $w_1^2+w_2^2 = 1$, Z_1 and Z_2 the test statistic for each stage.

- Z_1 is a test statistic for the individual hypothesis μ(1) = μ(4). Thus, if it holds μ(1) < μ(4), then the global hypothesis is also not true. Note that Z_1 could be regarded as a special case of a contrast test for H0: μ(1) = μ(2) = μ(3) = μ(4) where no participants are assigned to study arm 2 and 3.
- Z_2 is the multiplicity adjusted test statistic for the maximum of m contrast tests representing m candidate models, each testing the individual null hypothesis H0(m): c(m)' μ = 0. If one of the H0(m) is rejected locally, then the global hypothesis is also not true.

In case Z_1 or the corresponding observed difference between study arm 1 and 2 after Stage 1 is below a certain boundary (i.e., low treatment effect) the trial might be stopped for futility.

9.2 Sample Size Determination

Up to approximately 440 participants (100 in Cohort A + up to 340 in Cohort B) will be randomized, treated, and followed in this study.

Participants in Cohort A will be stratified by the following factors:

- Region (3 levels: North America and Western Europe vs Asia vs Central/South America and rest of the world),
- Disease diagnosis at Screening (2 levels: CLE [SCLE and/or DLE] vs SLE).

Participants in Cohort B will be stratified by the following factors:

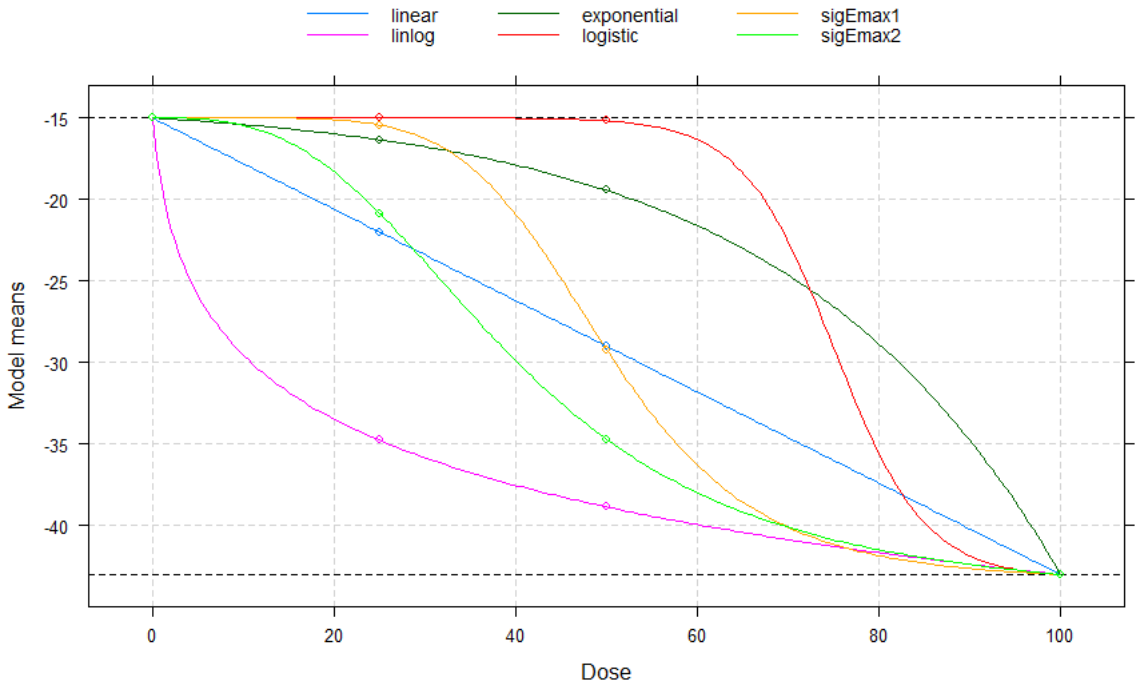
- Region (3 levels: North America and Western Europe vs Asia vs Central/South America and rest of the world),
- Biomarker status at Screening (2 levels: [IFN-GS high AND/OR positive RNA auto-antibodies: anti-SSA/Ro, SSB/La, Smith/RNP] vs [IFN-GS low AND negative RNA auto-antibodies: anti-SSA/Ro, SSB/La, Smith/RNP]).
- Hybrid SELENA-SLEDAI score at Screening (2 levels: ≥ 10 versus < 10).

This study is powered for establishing that the changes in doses of enpatoran lead to a difference in efficacy results in each cohort separately.

CLE (active SCLE and/or DLE) or SLE participants with predominantly active rash *(participants from cohort A)*: To establish the dose-response in percentage change from baseline in CLASI-A scores at Week 16 in participants with CLE (active SCLE and/or DLE) or SLE with predominantly active rash, a multiple comparison procedure (MCP) approach (Bretz 2005) was used, which calculates combined (average) power across several pre-defined parametric dose-response functional models. Family wise type I error rate is controlled while performing multiple comparisons, in which process the correlations among different models are considered.

Considering 4 doses levels (0-placebo, enpatoran 25 mg twice per day, enpatoran 50 mg twice per day and enpatoran 100 mg twice per day), with a randomization ratio of 1:1:1:1, a minimal percentage decrease from baseline in CLASI-A score at Week 16 of 15% and a maximum percentage decrease from baseline in CLASI-A score at Week 16 of 43%, a standard deviation of 35% and 6 candidate models (linear, exponential, linlog, logistic, SigEmax1 and sigEmax2) (see figure below) defined as:

- Linear
- Log-linear
- Exponential: $\delta = 30$
- Logistic: $E_0 = -15$ $E_{max} = -43$, $ED_{50} = 75$, $\delta = 5$
- SigEmax1: $E_0 = -15$ $E_{max} = -43$, $ED_{50} = 50$, $h = 6$
- SigEmax2: $E_0 = -15$ $E_{max} = -43$, $ED_{50} = 40$, $h = 3$



The power calculation is based on the estimated number of participants in the Full Analysis Set, considering an assumed withdrawal rate of 10%.

One hundred randomized participants, i.e. 25 in each of the 4 arms would allow 80% power to detect the underlying model, if the true difference in percent change in CLASI-A score between the highest dose and placebo is 28, assuming the standard deviation in this variable is 35 and allowing for family wise one-sided type I error rate of 0.025. To this purpose, 100 participants will be included in Cohort A.

Participants with Active SLE *(Participants from Cohort B)*: For the primary endpoint of BICLA response at Week 24, up to 340 patients will be randomized in 4 doses levels in cohort B. Simulations were performed in R to evaluate the power of detecting a dose-response relationship between the BICLA response rate at Week 24 and the 4 doses levels (placebo, enpatoran 25 mg twice per day, enpatoran 50 mg twice per day and enpatoran 100 mg twice per day) using the MCP-Mod approach. For these simulations, an overall randomization of 1:1:1:1 over 4 doses levels, with a 2:1 ratio for Part 1 (enpatoran 100 mg twice per day: Placebo) was considered, with a response rate of 25% in the Placebo dose level and a maximum response rate of 50% for the highest dose and a set of candidate models were defined similarly to the models described for Cohort A. These simulations taking into account the 2 stages of the cohort B design for hypothesis testing show an 80% power for detecting a dose-response, adjusting the overall p-value with an inverse normal method.

9.3 Analyses Sets

The analysis populations are specified below. The final decision to exclude participants from any analysis population will be made during a blinded data review meeting prior to database lock and unblinding. The following analysis set definitions will be considered for each cohort.

Analysis Set	Description
Screening (SCR)	All participants, who provided informed consent, regardless of the participant's randomization and study intervention status in the study.
Full Analysis Set (FAS)	All participants who were randomized to study intervention. Participants will be analyzed per the intervention group to which they were randomized, following the intention-to-treat principle.
Safety Analysis Set (SAF)	All participants, who were administered any dose of any study intervention. Participants will be analyzed per the actual study intervention they received.
PK	All participants, who receive at least 1 dose of study intervention, have no important events affecting PK, and provide at least 1 measurable post-dose concentration. Participants will be analyzed per the actual study intervention they received. All PK analyses will be based on this analysis set.
PD	All participants, who receive at least 1 dose of study intervention, have no important events affecting PD, and have a Baseline and at least 1 measurable PD endpoint post-dose. Participants will be analyzed per the actual study intervention they received. All PD analyses will be based on this analysis population.

The following subgroups of the FAS will be considered for exploratory analysis on selected efficacy analyses:

- Region as per randomization
- Disease Diagnosis as per randomization
- Race (Black, non-Black)
- Race (Asian, non-Asian)
- Ethnicity **(**Hispanic, non-Hispanic; Japanese, non-Japanese; Chinese, non-Chinese)
- Severity of disease at Screening
- Biomarker levels as per randomization ([IFN-GS high AND/OR positive RNA auto-antibodies: anti-SSA/Ro, SSB/La, Smith/RNP] vs [IFN-GS low AND negative RNA auto-antibodies: anti-SSA/Ro, SSB/La, Smith/RNP])
- IFN-GS levels at baseline (IFN-GS high, IFN-GS low)
- Age
- Gender

The list of subgroups will be finalized in the Integrated Analysis Plan (IAP).

In addition, the subgroup of SLE participants from Cohort B with CLASI-A ≥ 8 at Screening and confirmed at Day 1 will be analyzed for secondary and exploratory endpoints relative to active lupus rash.

9.4 Statistical Analyses

This section provides a description of the statistical methods to be used to analyze efficacy, safety, and other endpoints. Prior to locking the database, a detailed IAP will be finalized.

Unless otherwise specified, the FAS will be the primary analysis set for all efficacy analyses, PRO analyses, and reporting of demographic and Baseline characteristics. The Safety analysis set will be used for all safety data reporting.

Continuous variables will be summarized descriptively using the number of observations, mean, SD, median, first quartile (Q1), third quartile (Q3), minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages. The denominator for the percentages will be the total number of participants in the treatment group and analysis set being presented, unless otherwise specified (e.g., on some occasions, percentages may be calculated based on the total number of participants with available data at a particular time point).

Tests of treatment effect on each primary efficacy endpoint will be conducted at a one-sided α-level of 0.025. P-values and the two-sided 95% CIs will be presented where applicable. For secondary endpoints, p-values will be interpreted as nominal. Treatment comparisons for each data type are described in later sections. Alternative or additional statistical methods may be used as appropriate as outlined in the IAP.

Data from all investigative sites will be pooled for all planned analyses. Analysis of individual site findings or country findings will be considered if necessary. For those measures that are analyzed using change from Baseline scores, observed scores may also be presented descriptively.

The IAP will provide definitions of Baseline measurement for change from Baseline endpoints.

Treatment compliance will be assessed in terms of the percentage of the actual doses taken relative to the number of scheduled doses and summarized by descriptive statistics.

All participants will be included in individual subject data listings.

Any changes in the data analysis methods described in the protocol will require an amendment only if the change affects a principal feature of the protocol. Any other changes to the planned data analysis that does not require a protocol amendment will be described in the IAP and the CSR.

Additional exploratory analyses will be conducted as deemed appropriate.

9.4.1 Efficacy Analyses

Endpoints	Statistical Analysis Methods
Primary	
Percent change from baseline in CLASI-A at Week 16	This endpoint will be analyzed for CLE (active SCLE and/or DLE) and SLE participants from Cohort A as described in Section 9.4.1.1
BICLA response at Week 24	This endpoint will be analyzed for Cohort B SLE participants as described in Section 9.4.1.2
Secondary	
The following secondary endpoints will be analyzed for CLE (active SCLE and/or DLE) and SLE participants from Cohort A and Cohort B with CLASI-A ≥ 8 at Screening and confirmed at Day 1	
• Change from baseline in Cutaneous Lupus Activity Investigator's Global Assessment (CLA-IGA) at Week 16 and Week 24 • Change from baseline in Physician's Global Assessment of Cutaneous Lupus Disease at Week 16 and Week 24	MMRM analysis will be used to model the score at each visit through Week 24 with terms for intervention group, visit, intervention group by visit interaction, Baseline score and randomization strata. Test and treatment effect estimator (with 95% 2-sided CI) based on difference (enpatoran versus placebo) in least squares means of Week 24 %CFB (or CFB respectively) from the model. Cumulative distribution function for Week 24 CFB will be estimated by intervention group. Missing data assumed to be missing at random (MAR), with missing data status noninformative. Descriptive statistics will be provided at each visit.
• 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	These endpoints will be analyzed using the logistic regression model, with the covariates of the randomization stratification factors. Test and treatment effect estimator (with 95% 2-sided CI) will be based on the odds ratios (each enpatoran versus placebo) in participants with prednisone-equivalent dose ≥ 10 mg at Day 1. Descriptive statistics will be provided.
• 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 FACIT-Fatigue scores at Week 24	MMRM analysis where score CFB at each visit through Week 24 is modeled, with terms for intervention group, visit, intervention group by visit interaction, Baseline score and randomization strata. Test and treatment effect estimator (with 95% 2-sided CI) based on difference (enpatoran versus placebo) in least squares means of Week 24 CFB from the model. Cumulative distribution function for Week 24 CFB will be estimated by intervention group. Missing data assumed to be missing at random (MAR), with missing data status noninformative for CFB. Descriptive statistics will be provided at each visit.
The following secondary endpoints will be analyzed for SLE participants from Cohort B	
• SRI-4 response at Week 24 • LLDAS attainment at Week 24 • Remission attainment at Week 24 • 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.	These endpoints will be analyzed using the logistic regression model, with the randomization stratification factors as covariates. Test and treatment effect estimator (with 95% 2-sided CI) will be based on the odds ratio (each enpatoran versus placebo). Descriptive statistics will be provided at each timepoint through Week 24.

Endpoints	Statistical Analysis Methods
• 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	Same as above, restricted to participants with a CS prednisone-equivalent dose ≥ 10 mg at Day 1
• Change in the number of joints which are tender and swollen in 28-joint count from baseline at Week 24 • Change from baseline in Physician's Global Assessment at Week 24.	MMRM analysis where score CFB at each visit through Week 24 is modeled, with terms for intervention group, visit, intervention group by visit interaction, Baseline score and randomization strata. Test and treatment effect estimator (with 95% 2-sided CI) based on difference (enpatoran versus placebo) in least squares means of Week 24 CFB from the model. Cumulative distribution function for Week 24 CFB will be estimated by intervention group. Missing data assumed to be missing at random (MAR), with missing data status noninformative for CFB. Descriptive statistics, including actual values and CFB at each visit through Week 24.
• 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.	Time to event endpoints will be analyzed with a stratified logrank test of distribution of time to the event with strata defined by randomization strata will be used. Estimation of treatment effect (and 95% 2-sided CI) based on hazard ratio from stratified Cox model of event hazard rate, with terms for intervention group, and strata defined by randomization strata. Cumulative distribution function for time to event will be estimated via Kaplan-Meier method by intervention group. Censoring assumed to be noninformative for event. A participant discontinuing treatment early without flare will have be censored at the last time point at which flare could be assessed (i.e. treatment discontinuation date). A participant taking protocol-prohibited medication(s), as determined by EAC, prior occurrence of flare will be considered as having an event on the date of starting protocol-prohibited medication(s). A participant completing the 52 Week treatment period without severe flare will be censored at Week 24.
• Change from Baseline in the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores at Week 24.	MMRM analysis where score CFB at each visit through Week 24 is modeled, with terms for intervention group, visit, intervention group by visit interaction, Baseline score and randomization strata. Test and treatment effect estimator (with 95% 2-sided CI) based on difference (enpatoran versus placebo) in least squares means of Week 24 CFB from the model. Cumulative distribution function for Week 24 CFB will be estimated by intervention group. Missing data assumed to be missing at random (MAR), with missing data status noninformative for CFB. Descriptive statistics, including actual values and CFB at each visit through Week 24.
Exploratory Endpoints	Will be specified in the Integrated Analysis Plan finalized before database lock.

9.4.1.1 Primary Analysis of Percent Change in CLASI-A at Week 16

Per ICH E9 (R1), Addendum on Estimands and Sensitivity Analysis in Clinical Trials (November 2019), the primary estimand targeting this primary objective is defined by the following attributes:

- **Variable (endpoint):** The primary endpoint is the percentage change in CLASI-A at Week 16. Measurements at the participant level are the CLASI-A scores during the course of the treatment period
- **Treatment:** The intervention of interest is enpatoran during the treatment period and placebo during the treatment period.
- **Population:** The population of patients targeted by the clinical question is patients with CLE (active SCLE and/or DLE) or SLE with predominantly active rash (defined as patients with SCLE, DLE or SLE and a CLASI-A score at ≥ 8 at Screening and confirmed at Day 1).
- **Strategies for handling intercurrent events:** The main intercurrent events envisaged are: early discontinuation of assigned treatment, protocol-prohibited medications as confirmed by EAC (i.e., new or increased immunosuppressives or antimalarials), corticosteroid use not compliant with protocol rules as determined by EAC. The strategy for dealing with these is the treatment policy.
- **Population-level summary:** The population-level summary comparing the intervention groups is the LS mean estimate of mean percent change from baseline score (SE), difference of the LS mean from placebo, and 2-sided 95% CI of the difference.

The primary efficacy analysis of this estimand will be conducted on the FAS population, in participants in Cohort A.

A Multiple Comparison Procedure – Modeling (MCP-Mod) approach will be used to analyze the primary efficacy variable, i.e. percent change from baseline in CLASI-A at Week 16.

Set of candidate models (for MCP and Mod step): A dose-effect will be detected if at least one of the candidate models is significant, with a one-sided family wise error rate of 2.5% accounting for the set of models. Specifically, the approach calculates for each candidate model optimal contrast and identifies significant dose-response models, if exists. If an optimal contrast is significant (i.e. positive proof-of-concept), a dose-response relationship can be established.

The procedure on how to perform model selection: The candidate model that fits the data best (e.g. smallest AIC statistic) will be chosen for dose-estimation. The mean difference of each active study intervention arm to placebo together with its 95% confidence interval and p-value will be estimated.

As a sensitivity analysis, a linear mixed effect model for repeated measure with region, study intervention and time as a classification variables, and baseline CLASI-A, as a covariate, and treatment by time interaction will be used on the FAS to estimate the percent change from baseline in CLASI-A at each time point and differences to placebo, with a Dunnett adjustment to account for multiple comparisons at each time point. The mean difference to placebo, Dunnett-adjusted confidence interval and Dunnett-adjusted p-value will be provided.

Sensitivity analyses on the handling of intercurrent events use of protocol-prohibited medications and non-compliance with CS tapering rules that may impact the primary endpoint will be detailed in the IAP, in line with the hypothetical strategy.

9.4.1.2 Primary Analysis of the Response in BICLA at Week 24.

The primary estimand targeting this primary objective is defined by the following attributes:

- **Variable (endpoint):** The primary endpoint is the Response in BICLA at Week 24 defined by:
    1. BILAG 2004 improvement (all A scores at Baseline improved to B/C/D, and all B scores improved to C or D),
    2. No worsening in disease activity (no new BILAG 2004 A scores and ≤ 1 new B score) from baseline,
    3. No worsening of total hybrid SELENA-SLEDAI score from Baseline,
    4. No significant deterioration (< 10% worsening) in visual analog PGA from baseline
- **Treatment:** The intervention of interest is enpatoran during the treatment period and placebo during the treatment period.
- **Population:** The population of patients targeted by the clinical question is patients with active SLE.
- **Strategies for handling intercurrent events:** The main intercurrent events envisaged are early discontinuations of assigned treatment, the prohibited-protocol treatments as confirmed by the EAC (i.e. new or increased immunosuppressives or antimalarials), corticosteroid use not compliant with protocol rules as determined by EAC. The strategy for dealing with these is the composite variable strategy. A participant with any of these intercurrent events will be considered as non-responder from the start of the intercurrent event.
- **Population-level summary:** The population-level summary comparing the intervention groups is the proportion of participants achieving BICLA response at Week 24 (95 % CI).

The primary efficacy analysis will be conducted on the FAS population, in participants with active SLE (Cohort B).

A Multiple Comparison Procedure – Modeling (MCP-Mod) approach will be used to analyze the primary efficacy variable, i.e. proportion of participants achieving BICLA response at Week 24 with a similar approach to the one described for the primary endpoint of percent change from Baseline in CLASI-A.

Odds Ratio and associated two-sided 95% CI comparing each dose level to Placebo based on a logistic models for the odds of a given BICLA response in the appropriate population, with treatment arm as a factor and adjustment for covariates base on randomization strata will be presented.

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis population, reported for participants with CLE (participants from Cohort A with active SCLE and/or DLE) and SLE (participants from Cohort B and selected participants with SLE from Cohort A) separately.

Endpoint	Statistical Analysis Methods
Primary	Not Applicable
Secondary	
Adverse Events	Descriptive statistics, AESI summaries, 3-Tier AE summaries
Clinical Laboratory Test Values	Descriptive statistics, shift tables, boxplots, individual participant line plots, Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) figures
ECG Parameters	Descriptive statistics
Vital Signs	Descriptive statistics
Tertiary/Exploratory	Not applicable

9.4.2.1 Adverse events

Adverse events will be coded using the MedDRA. All Treatment-emergent AEs (TEAEs) will be summarized by intervention group. Treatment-emergent AEs are defined as AEs that occurred or worsened on or after the first dose of study intervention. The number and percentage of participants who experienced at least 1 TEAE will be summarized by System Organ Class and preferred term. The percentage will be based on the number of participants in each intervention group. Treatment-emergent AEs will also be summarized by relationship to intervention and by severity within each intervention group. Deaths, SAEs, AESIs, and AEs leading to study discontinuation will be tabulated and presented in data listings. Participant level data listings of all AEs will be presented.

Summary and analysis of AEs will be performed based on the 3-tier approach (Crowe 2009) as further detailed in the IAP. Tier 1 AEs and AESIs will be predefined in the IAP.

9.4.2.2 Clinical Laboratory Test Values

Clinical laboratory results (chemistry, hematology, and urinalysis) will be summarized using descriptive statistics for each visit by intervention group. Observed values at each visit and changes from Baseline to each post-Baseline visit will be presented. For clinical laboratory parameters with associated normal ranges, number and percentage of participants having high/low/normal findings for worst on-treatment laboratory value will be summarized by intervention group; shift tables will be used to summarize changes from Baseline finding to worst on-treatment finding. For clinical laboratory parameters with National Cancer Institute (NCI)-CTCAE grades, shift tables will be used to summarize changes from Baseline grade to worst on-treatment grade. The distribution of selected laboratory parameters by time point and intervention group will be displayed via boxplots. Line plots of LH, FSH and testosterone will be provided for male participants. All laboratory data will be provided in participant data listings.

Analyses of liver enzyme tests will include Kaplan-Meier estimates of time to ALT or AST events, plots supporting evaluation of Drug-Induced Serious Hepatotoxicity (eDISH), and individual participant profiles.

9.4.2.3 Vital Signs

Observed values at each visit and changes from Baseline to each post-Baseline visit in vital signs (blood pressure, pulse rate, respiratory rate, and temperature) will be summarized by time point and intervention group using descriptive statistics. Similar summaries of descriptive statistics will be provided for the vital signs collected before and after the first dose of study intervention. Out-of-range values of vital signs will be tabulated as appropriate. All vital signs will be provided in participant data listings.

9.4.2.4 Electrocardiogram Parameters

Observed values at each visit and change from Baseline to the end of treatment period in ECG parameters (e.g., PR, HR, QRS, RR, QT, and QTcF) will be summarized by intervention group using descriptive statistics. QTc will be reported based on Fridericia's method. Percentage and counts of participants with normal and abnormal ECG findings will be summarized by intervention group.

Out-of-range values of ECG parameters will be tabulated as appropriate. All ECG data will be provided in participant data listings.

For all ECG parameters, the results for categorical analysis will be summarized by intervention group and visit (or time point) in frequency tables with counts and percentages of participants. Categories will cover absolute values and changes from Baseline (predose Day 1):

HR:

- Absolute < 50 bpm, < 40 bpm, < 30 bpm
- Change from Baseline > 20 bpm, > 30 bpm, > 40 bpm

PR:

- Absolute > 200 ms and > 220 ms
- Change from Baseline > 30 ms

QRS:

- Absolute > 110 ms

QTcF:

- Absolute > 450 ms, > 480 ms, and > 500 ms
- Change from Baseline > 30 ms and > 60 ms

Electrocardiogram parameters will be summarized using descriptive statistics for continuous variables such as QTcF intervals, and frequency counts and percentages for categorical variables.

9.4.2.5 Concomitant Medication and Procedures

Prior and concomitant medications will each be categorized by therapeutic class and preferred term using WHO Drug coding dictionary. The number and percent of participants using each prior and concomitant medication will be summarized by therapeutic class and preferred drug name for each intervention group. Participants who reported more than 1 medication for a particular preferred term will be counted once for each preferred term and therapeutic class. Concomitant procedures will be categorized by ATC class and preferred term using MedDRA. The number and percent of participants experiencing each prior and concomitant procedure will be summarized by type of procedure for each intervention group.

9.4.3 Other Analyses

9.4.3.1 Pharmacokinetic Parameters, Pharmacodynamic parameters

In general, biomarkers and PD parameters assessed at planned visits and premature early discontinuation from treatment will be summarized in a manner similar to safety laboratory parameters.

Pharmacokinetic analysis will be performed on the Pharmacokinetic Analysis Set for each cohort. Plasma concentrations (and PK parameters using noncompartmental methods, as appropriate) will be listed and summarized by study day (and time window, as appropriate) and dose group.

The PK of enpatoran and exposure-response relationships with respect to biomarkers/clinical efficacy and safety endpoints will be described using modeling and simulation and may include data from other enpatoran studies. Full details of the relevant (integrated) population modeling and simulation activities (including objectives, relevant endpoints, used study data, methodology, software, etc.) will be defined in a separate pharmacometric analysis plan (PMAP). The results of the corresponding analyses will be reported separately from the study CSR.

Details on the exploratory Pk and biomarkers analyses will be specified in the Integrated Analysis Plan, which will be finalized before database lock.

9.4.3.2 Demographics, Baseline Characteristics, Disposition and Compliance.

Participant's demographics, such as age, gender, race, will be summarized by study intervention group using descriptive statistics. Baseline disease characteristics will also be summarized by study intervention group.

Disposition of participants (i.e., discontinuation from treatment by reason, discontinuation from study by reason) and compliance of participants to intervention will be summarized by intervention group using descriptive statistics.

These summaries may be repeated for subgroups of participants, such analyses will be detailed in the IAP.

9.4.3.3 Patient-Reported Outcomes

Change from Baseline in PRO scores at a given time point will be compared between enpatoran doses and Placebo in the relevant selection of participants via a MMRM adjusted for Baseline PRO score and covariates defined by randomization strata. The adjusted difference in least-squares mean for the change from Baseline at a given time point, 2-sided 95% CI, and p-value will be reported. A similar analysis will be performed for all PRO score change from Baseline endpoints.

9.4.4 Sequence of Analyses

Interim analyses listed below will be performed by independent statistical data center(s) in an unblinded fashion and the data will be evaluated by the external IDMC and the Sponsor's internal unblinded Firewall team independent of the study team. The study team will remain blinded. Prior to the first interim analysis, a detailed Interim Analyses Plan and Firewall charter as appropriate will be finalized, specifying at minimum the details such as the timing of the Interim Analyses, the endpoint(s) that will be analyzed, decision rules, and study adjustments as well as the process flow in order to maintain the appropriate study blinding and integrity.

Details of the primary and final analyses will be described in the IAP. Details of the IDMC analyses, will be described in the Interim Analysis Plan and the IDMC Charter and related documentation.

There may be up to three planned interim analyses:

Interim analysis for futility (Cohort A): taking into consideration enrollment into the 2 cohorts, the Sponsor may decide to perform an interim analysis to evaluate the early clinical and pharmacodynamic responses for futility in Cohort A, with no pause in the enrollment before the interim analysis planned for Cohort B adaptations.

Interim analyses for futility and adaptation (Cohort B Part 1): after the 60 SLE participants from Cohort B Part 1 have completed at least 12 weeks of treatment (or discontinued earlier), the following analyses are planned:

- The first analysis will be performed on the 60 participants from Cohort B Part 1 in SLE patients when they have reached at least 12 weeks of treatment to decide on whether to terminate Cohort B for futility or potentially adapt Cohort B Part 2 dose levels and randomization ratio based on pre-specified decision framework, as defined in the Interim Analysis Plan. The difference in Week 12 BICLA response in all participants included in the analysis and the difference in Week 24 BICLA response in all participants who reached this timepoint comparing the enpatoran 100 mg twice per day dose to Placebo will be estimated together with a two-sided 95% confidence interval, along with other supportive information on available efficacy, safety, PK and PD data.
- A second analysis will be conducted at the same time, to support potential adaptation of Cohort B Part 2 dose levels (not exceeding the highest clinically investigated dose) and randomization ratio. This analysis will leverage dose/exposure-response analyses of participants from Cohort A (CLE and SLE patients across 25 to 100 mg twice daily dose levels), from Cohort B Part 1 (SLE patients at 100 mg twice daily) and from a currently ongoing Phase Ib study in SLE and CLE (NCT04647708). This analysis will provide the

Sponsor the opportunity to evaluate whether the accumulating clinical data support the partial or complete translation of dose/exposure-response information from CLE to SLE setting and inform the potential implementation of alternative dose levels in Cohort B Part 2.

Primary analysis (Cohort A): performed after all participants in Cohort A complete 16 weeks of treatment or discontinue treatment early.

Final analysis of Cohort A and Cohort B: performed after all participants completed the Safety follow-up of the DBPC period (if not rolled over to the LTE study) or have discontinued early the study or have rolled over to a LTE study as part of a separate Sponsor protocol. The DBPC period database will be locked, and the drug codes will be broken and made available for analysis. All endpoints based up to Week 24 data will be evaluated.

In addition, analyses will be performed at regular intervals for the purpose of safety monitoring by the IDMC.

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11 Appendices

Appendix 1 Abbreviations

ACR	American College of Rheumatology
AE	Adverse Event
AESI	Adverse Events of Special Interest
BICLA	BILAG-Based Composite Lupus Assessment
BILAG	British Isles Lupus Assessment Group
C-SSRS	Columbia-Suicide Severity Rating Scale
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CLE	Cutaneous Lupus Erythematosus
CNS	Central Nervous System
CRF	Case Report Form
CRO	Clinical Research Organization
CS	Corticosteroids
CSR	Clinical Study Report
DBPC	Double-Blind Placebo-Controlled
DF	Dose-finding
DLE	Discoid Lupus Erythematosus
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
EAC	Endpoint Adjudication Committee
EudraCT	European Clinical Trials Database
EULAR	European League Against Rheumatism
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full Analysis Set
FIH	First in Human
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HRT	Hormone Replacement Therapy
IAP	Integrated Analysis Plan
IB	Investigator's Brochure

ICF	Informed Consent Form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFNs	Interferons
IRB	Institutional Review Board
IVRS	Interactive Voice Responsive System
IWRS	Interactive Web Responsive System
LLDAS	Lupus Low Disease Activity State
LTE	Long-term Extension
MCP-Mod	Multiple Comparison Procedure – Modeling
MMRM	Mixed model with repeated measures
PD	Pharmacodynamic
PK	Pharmacokinetic
PoC	Proof of Concept
PRO	Patient-Reported Outcome
QoL	Quality of Life
QTcF	QT Interval Corrected Using Fridericia's Formula
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SCLE	Subacute Cutaneous Lupus Erythematosus
SELENA	Safety of Estrogens in Systemic Lupus Erythematosus National Assessment
SLE	Systemic Lupus Erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus International Collaborating Clinics
SoA	Schedule of Activities
SRI	Systemic lupus erythematosus Responder Index
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	Tuberculosis
TEAE	Treatment-emergent Adverse Events
TLR	Toll-like Receptor

ULN	Upper Limit of Normal
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential
VAS	Visual Analog Scale

Appendix 2 Study Governance

Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information, as requested, for the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. This information is required during the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative (where allowed by local laws and regulations) and answer all questions on the study.
- Participants will be informed that their participation is voluntary.
- Participants or their legally authorized representative (where allowed by local laws and regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; the Japanese ministerial ordinance on GCP; local regulations; ICH guidelines; HIPAA requirements, where applicable; and the IRB/IEC or study center. In Japan, a subject information sheet in the local language and prepared in accordance with Japan's GCP and the Note for Guidance on GCP (ICH Topic E6, 1996) will be provided by the Sponsor for the purpose of obtaining informed consent.
- The medical record will include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent will also sign the ICF.
- If the ICF is updated during their participation in the study, participants will be re-consented to the most current, approved version.
- Participants who are rescreened are required to sign a new ICF.

Data Protection

- The Sponsor will assign a unique identifier to participants after obtaining their informed consent. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.
- The Sponsor will inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure will also be explained to the participant and pregnant partners (if applicable), who will be required to give consent for their data to be used, as specified in the informed consent.
- The participant will be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.

Study Administrative

- The study will be conducted at approximately 130 sites in approximately 20 countries in an outpatient basis.
- The Coordinating Investigator listed on the title page represents all Investigators for decisions and discussions on this study, per ICH GCP. The Coordinating Investigator will provide expert medical input and advice on the study design and execution and is responsible for the review and signoff of the clinical study report.
- An Independent data monitoring committee (IDMC) will be established to assess safety and tolerability of study intervention during the conduct of the study; IDMC will also review the interim analyses (IA) to make recommendations on the conduct of the study and if needed, adaptive elements for Cohort B (see Section 4.3). The IDMC will be composed of a minimum of three members who do not have any conflict of interests with the study Sponsor, including two clinicians and a biostatistician. The full membership, mandate, and processes of the IDMC will be detailed in the IDMC charter. The IDMC will monitor the study until the last participant has completed the Safety Follow-Up Visit following the DBPC Treatment Period or has entered into the LTE study under separate study protocol.
- The Firewall Team will be comprised of relevant Sponsor senior experts (as described in a dedicated Firewall charter), who are independent of the study team, to review the IDMC recommendation(s) with regards to the conduct and adaptive elements of the trial design, based on unblinded data as appropriate.
- An Endpoint Adjudication Committee (EAC) will be formed to review blinded data for the primary and secondary endpoints (e.g., reduction of disease activity, lupus flares, etc.) to monitor the quality of the SLE assessments by Investigators. The EAC will also adjudicate treatment failures, monitor the use of concomitant medications (especially, CS), and review participant withdrawal criteria. This EAC will comprise at least 2 physicians with expertise in SLE clinical studies and not participating in this study. Sponsor and CRO representatives are eligible for membership on the EAC. Details regarding the EAC will be provided in a separate EAC charter.
- A Study Steering Committee (SSC) will ensure that the study meets scientific standards and provide direction and oversight to the study from an Investigator's perspective, including protocol creation and amendments, study execution, and evaluation of study results at the end of study. Investigators in this clinical study and other experts who are not otherwise involved in the trial may serve on this committee.
- IQVIA will provide CRO services and Q2 solutions will serve as central laboratory.
- Sponsor will be responsible for supply and manufacture of study intervention (enpatoran and placebo).
- The study will appear in the following clinical studies registries: EudraCT number 2021-004648-27.

Details of structures and associated procedures will be defined in a separate Study Manual.

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
  - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - For studies with Japanese sites, the Japanese ministerial ordinance on GCP
  - Applicable laws and regulations
- The protocol, protocol amendments (if applicable), ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) will be submitted to an IRB/IEC for review and approve before the study is initiated.
- For studies with Japanese sites, the Sponsor initiates the study at a site after obtaining written approval from the Head of the study site, based on favorable opinion/approval from the concerned IRB.
- Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.
- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to participants for use during the study. These provide the means for participants to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the participant. The information on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).
- The first point of contact for all emergencies will be the clinical study Investigator caring for the participant. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard process established for Investigators.
- When the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor (or designee) physician. This includes provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor (or designee) physician to assist with the medical emergency and to provide support for the potential unblinding of the participant concerned.

Clinical Study Insurance and Compensation to Participants

- Insurance coverage will be provided for each country participating in the study. Insurance conditions will meet good local standards, as applicable.
- In Japan, the Sponsor is entirely responsible for AEs that are associated with this study and cause damage to the health of the participants, except for AEs caused by an intentional and/or significant deviation on the part of the Investigator, the study site, and/or the participants. The Sponsor will provide insurance to fulfill this responsibility.

Clinical Study Report

- After study completion, the Sponsor will write a clinical study report in consultation with the Coordinating Investigator, and any Steering Committee or other relevant study-appointed committees or groups.

Publication

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows Merck to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.
- Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- After completion of the study, a CSR will be written by the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3 and will be submitted in accordance with local regulations.
- Any and all scientific, commercial, and technical information disclosed by the Sponsor in this protocol or elsewhere should be considered the confidential and proprietary property of the Sponsor. The Investigator shall hold such information in confidence and shall not disclose the information to any third-party except to such of the Investigator's employees and staff who had been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The Investigator shall not use such information for any purpose other than for determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.
- The Investigator understands that the information developed from this clinical study will be used by the Sponsor in connection with the development of the study intervention and therefore may be disclosed as required to other clinical Investigators, to the USA Food and Drug Administration, and to other government agencies. The Investigator also understands that, to allow for the use of the information derived from the clinical study,

the Investigator has the obligation to provide the Sponsor with complete test results and all data developed in the study.

- No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement
- The first publication will include the results of the analysis of at least the primary endpoints and will include data from the study site. The Investigator will inform the Sponsor in advance about any plans to publish or present data from the study. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require review by the Sponsor before submission. The Sponsor will not suppress publication but maintain the right to delay publication to protect intellectual property rights.
- Posting of data on the European Clinical Trial Database (EudraCT) and www.ClinicalTrials.gov is planned and will occur 12 months after the last visit, or scheduled procedure, or another appropriate date to meet applicable requirements.

Data Quality Assurance

- All participant study data will be recorded on printed or electronic CRFs or transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the CRF. Details for managing CRFs are in the Study Reference Manual.
- For PRO data (e.g., Quality of life [QoL] and pain assessments), ePRO will be used.
- The Investigator will maintain accurate documentation (source data) that supports the information in the CRF.
- The Investigator will permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.
- QTLs will be pre-defined in the Quality Risk Management Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are in the Monitoring Plan .
- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. Details will be outlined in Data Management documents and procedures.

- Study Monitors will perform ongoing source data verification to confirm that data in the CRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, the Japanese ministerial ordinance on GCP, and all applicable regulatory requirements.
- The Investigator will retain records and documents, including signed ICFs, pertaining to the conduct of this study for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

Source Documents

- Source data is defined as all data in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study that are necessary for the reconstruction and evaluation of the study.
- The SDV process is described in a separate manual.
- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.
- The Investigator will maintain source documents that support the data recorded in the CRFs.
- Data recorded on CRFs that are transcribed from source documents will be consistent with the source documents or the discrepancies will be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records will be available.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval. In Japan, the head of the study site must retain all records, including documents and data, which relate to the clinical study in accordance with GCP. The head of the study site must retain the records at the site (hospital, research institute, or practice) for the longest possible time permitted by Japan's GCP, and/or as per ICH GCP guidelines, whichever is longer. In any case, the head of the study site should ensure that no destruction of medical records is performed without the written approval of the Sponsor.
- Definition of what constitutes source data is found in the CRF guidelines.

Study and Site Start and Closure

The study start date is when the first participant signs the Informed Consent Form.

Study and Site Closure

The Investigator may initiate site closure at any time, provided there is reasonable cause and enough notice is given in advance of the intended closure.

Reasons for the early closure of a study site by the Sponsor or Investigator may include:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further development of the Sponsor’s compound
- If a new safety or efficacy information leads to an unfavorable risk benefit judgment for enpatoran
- If the IA indicates that the study is unlikely to achieve the primary endpoint at the time of the primary analysis
- If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any third-party service providers of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator will promptly inform the participants and assure appropriate participant therapy and/or follow-up.

In addition, the clinical study may be terminated prematurely or suspended at the request of Health Authorities.

Health Authorities and Independent Ethics Committees (IECs) or Institutional review Board (IRBs) will be informed about the discontinuation of the study in accordance with applicable regulations.

Appendix 3 Contraception and Barrier Requirements

Woman of Childbearing Potential (WOCBP):

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile, as specified below.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, consider additional evaluation.

Postmenopause:

Postmenopause is defined as no menses for 12 months without an alternative medical cause.

- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in a female not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
- A female on HRT and whose menopausal status are in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Permanent Sterilization:

For this study, permanent sterilization includes:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Documentation can come from the site personnel's review of the female's medical records, medical examination, or medical history interview.

For a female with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), Investigator discretion applies to determine study entry.

Table 4 Contraception Guidance

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods That Have Low User Dependency • Implantable progestogen-only hormone contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion Vasectomized partner: a highly effective contraceptive method provided that the partner is the sole sexual partner of a WOCBP, and the absence of sperm has been confirmed. Otherwise, use an additional highly effective method of contraception. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That are User Dependent
• Progestogen-only hormone contraception associated with inhibition of ovulation
  • Oral
  • Injectable
• Sexual abstinence: a highly effective method only if defined as refraining from intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study.

Notes: Contraceptive use by men or women is consistent with local regulations on the use of contraceptive methods for clinical study participants. Highly effective methods are those with a failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. Acceptable methods are considered effective, but **not** highly effective (i.e., have a failure rate of ≥ 1% per year). If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are **not** acceptable methods of contraception for this study. Male condom and female condom cannot be used together (due to risk of failure from friction).

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

AE Definition

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether considered related to the study intervention or not.
- An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline and are judged to be more severe than expected for the participant's condition are considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease, but may be leading to study intervention discontinuation).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or a SAE. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or a SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Unless judged by the Investigator to be more severe than expected for the participant's condition, any clinically significant abnormal laboratory findings, other abnormal safety assessments that are associated with the underlying disease, the disease/disorder being studied within the expectedness for participant's condition, as judged by the Investigator.
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the surgical procedure is the AE.
- SLE flares are not to be reported as an AE unless considered as unexpected in the context of the subject's medical history. The AE reported verbatim should describe the event term

instead of reporting an AE term of "SLE flare" unless it is unavoidable. SLE flares meeting SAE reporting criteria are always reported, whether or not it is consistent with the subjects' prior history. As for SAE reports, the SAE report should describe the events, and avoid reporting an SAE term of "SLE flare".

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Other Adverse Events to be Reported Using a Specialized Procedure or Form

- All pregnancies occurring during the study and their outcome will be documented on the Pregnancy report form and Parent-Child/Fetus Adverse Event Report form as outlined in Section 8.3.4.
- The following procedures should be followed for reporting overdoses (refer to CRF guidelines for further details):
  - Overdoses without an AE should be reported using the paper SAE Overdose Report form only, stating if the overdose was accidental or intentional.
  - Overdoses associated with a non-serious AE must be recorded on the AE CRF and also the paper SAE Overdose Report form. Overdoses associated with an SAE must be recorded on the AE CRF and the paper SAE Report form.

SAE Definition

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE is to be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization must be documented and reported as SAEs.

d. Results in persistent disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is **not** intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment will be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events are usually to be considered as serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- SLE disease flare meeting criteria of SAEs will be reported whether or not it is consistent with the subjects' prior history except planned hospitalization due to SLE flare.

Any suspected transmission of an infectious agent via a study intervention is also considered an SAE for reporting purposes, as specified below for reporting SAEs, AESIs.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator must record all relevant AE/SAE information in the CRF.
- As needed, Sponsor/designee may ask for copies of certain medical records (e.g., autopsy reports, supplemental lab reports, documents on medical history/concomitant medications, discharge letters), as supporting source documentation. All participant identifiers, except the participant number, must be redacted on these copies before submission to Sponsor/designee.

- The Investigator must attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) must be documented as the AE/SAE.
- Specific guidance is in the CRF Completion and Monitoring Conventions.

Assessment of Intensity

The Investigator will assess the intensity of each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. Do not confuse an AE that is assessed as severe with a SAE. Severe is a category used to rate the intensity of an event; both AEs and SAEs can be assessed as severe.

  An event is defined as "serious" when it meets at least 1 of the predefined criteria specified in the definition of an SAE, NOT when it is rated as severe.

If death occurs, the primary cause of death or event leading to death will be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this specific event and death will not be recorded as separate event. Only, if no cause of death can be reported (e.g., sudden death, unexplained death), the death per se might then be reported as an SAE.

Assessment of Causality

- The Investigator will assess the relationship between study intervention and each AE/SAE occurrence:
  - Unrelated: Not reasonably related to the study intervention. AE could not medically (pharmacologically/clinically) be attributed to the study intervention. A reasonable alternative explanation will be available.
  - Related: Reasonably related to the study intervention. AE could medically (pharmacologically/clinically) be attributed to the study intervention.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator must use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration must be considered and investigated.

- The Investigator must also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and assessed causality.
- There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor or its designee. To meet the reporting timeline, the causality assessment is not required for the initial report.
- The Investigator may change his/her causality assessment after considering follow-up information and must then send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator must perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by Sponsor/designee to elucidate the nature and/or causality of the AE or SAE, as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Sponsor/designee with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to Sponsor within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting by an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE in multicenter studies to the Sponsor or its designee is the electronic data collection tool.
- If the electronic system is unavailable, then the site must use the paper SAE form, specified below, to report the event within 24 hours.
- The site must enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-

line, then the site can report this information on a paper SAE form or to the Sponsor's safety department.

- By exception, an SAE (or follow-up information) may be reported by telephone. The site will complete the electronic SAE data entry immediately thereafter.

SAE Reporting by a Paper Form

- SAE reporting on a paper report form may be used in single center studies in addition to the standard electronic CRF and as a back-up method for an EDC system failure. The form includes completion instructions for the Investigator, names, addresses, and telephone and fax numbers. All information from the paper form will be transcribed into the electronic form as soon as the system becomes available.
- Facsimile transmission (fax to mail) of the paper form or any follow-up information is the preferred method for transmission and will be done within 24 hours to the Sponsor or its designee.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the form within 24 hours after becoming aware of the event.
- Additional documents (e.g. laboratory reports, autopsy report, hospital discharge letter) and relevant pages from the CRF may be required in addition (e.g. medical history, concomitant medication). The data provided will be consistent with the information in the CRF.

Reporting of AESIs

- For a non-serious AESI, the site must complete the specific AESI report form and notify the Sponsor immediately (within 24 hours), using the same process for reporting SAEs, as specified above.
- For a serious AESI, the site must complete an SAE report form, using the SAE reporting process, specified above.

Reporting of Pregnancies

- Pregnancy will be reported whether related to the study intervention using the applicable paper form.
- The applicable form will be used to report if an abnormal outcome of the pregnancy occurs and the child/fetus sustains an event.
- Facsimile transmission (fax to mail) of the paper form or any follow-up information is the preferred method for transmission and must be done within 24 hours to the Sponsor or its designee.

Appendix 5 Clinical Laboratory Tests

The protocol-required clinical laboratory assessments are in the following table:

Table 5 Clinical Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet count		MCV	White Blood Cell Count with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
	Hemoglobin		MCH	
	Hematocrit		ESR, CRP	
			Coagulation profile (INR, PT, aPTT, etc.)	
Biochemistry	Blood Urea Nitrogen	Potassium	Aspartate aminotransferase Alanine aminotransferase	Bilirubin
	Creatinine	Sodium	Gamma-glutamyl-transferase	Total Protein
	Glucose	Calcium	Alkaline phosphatase	eGFR
	Chloride	CO_2	Albumin	
Reproductive Hormones (male participants only)	Total Testosterone	LH	FSH	
First morning Clean-Catch Urinalysis	Frequent reminders/instructions must be provided to ensure the urine specimen is a clean-catch from the first morning void. Urinalysis will be performed by the local laboratory. The test may be repeated in clinic if sample determined to be a "dirty urine". • UPCR - Before morning of collection, provide participant with specimen cup. The participant will collect first morning void, clean-catch midstream sample at home in the morning of clinic visit and bring to the site. The sample will be sent to the central laboratory. The same sample taken for UPCR may be used to perform the urinalysis. • Specific gravity. • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick. • Microscopic examination (if blood, leukocyte esterase or protein is abnormal).			
Other Screening Tests	• FSH and estradiol (for non-WOCBP **only**). • Serum hCG pregnancy test (as needed for a WOCBP). • Serology: hepatitis B (HBs antigen, HBsAb, HBcAb with reflexive HBV DNA NAAT) and hepatitis C (HCVAb and reflexive HCV RNA NAAT), per exclusion criteria. • HIV laboratory test (either antibody or nucleic acid amplification test) • Tuberculosis assessment (QuantiFERON, T-SPOT). • Antinuclear antibodies. • Thyroid stimulating hormone.			
All study-required laboratory assessments will be performed by a central laboratory, except for urinalysis and microscopy, and urine pregnancy tests.				
PK	See Section 8.4			
Pregnancy test after Screening	Urine pregnancy test.			

Laboratory Assessments	Parameters
Other tests	
Amylase/lipase	At Screening and Day 1 only. Additional tests may be assessed as clinically indicated (per Investigator's judgment). Reflex amylase isoenzymes will be tested only when total amylase level is elevated.
Chest imaging	CXR, CT, MRI
SARS-CoV-2 test	Only if applicable (See Section 5.2)
Vaccine immunization status	Antibody titers to tetanus toxoid, diphtheria toxoid, pneumococcal antigens, and SARS-CoV-2
BILAG-2004 associated laboratory tests	Anticardiolipin, lupus anticoagulant, haptoglobin, and Coombs. The anticardiolipin, lupus anticoagulant, and haptoglobin blood specimens will be collected at all specified visits, however the blood will be stored at the central laboratory and the analyses performed only if the Investigator indicates that these tests need to be completed because of clinical suspicion of hemolytic anemia or antiphospholipid syndrome. Direct Coombs test samples will only be collected per the Investigator's opinion and applicable BILAG assessment requirements for determining hemolytic anemia.

aPTT = activated partial thromboplastin time, BILAG = British Isles Lupus Assessment Group, CT = computerized tomography, CXR = chest X-ray, eGFR = estimated glomerular filtration rate, FSH = follicle stimulation hormone, HCG = human chorionic gonadotropin, HBcAb = Hepatitis B core antibody, HBsAb = Hepatitis B surface antibody, HCVAb = Hepatitis C virus antibodies, HIV = human immunodeficiency virus, INR = international normalized ratio, LH = luteinizing hormone, MCH = mean corpuscular hemoglobin, MCV = mean corpuscular volume, MRI = magnetic resonance imaging, NAAT = nucleic acid amplification tests, PT = prothrombin time, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, UPCR = Urine protein: creatinine ratio, WOCBP = women of childbearing potential.

Appendix 6 Lupus Medication Guidance

Table 6 Medications with Required Washout

Medication type	Medications	Discontinuation (weeks) before the Screening Visit
CS	> 30 mg daily prednisone-equivalent, including but not limited to oral, topical CS Class IV, intramuscular, or injectable CS	2
	Intralesional therapies	4
NSAIDs	Above maximum prescribed dose per local label	2
Medications associated with AOX inhibition	Raloxifene, tamoxifen, quetiapine, estradiol, and derivatives (*For female lupus participants who are taking estrogen-containing contraceptives, will require switching to an alternative contraceptive method during the Screening period [≥ 4 weeks prior to Day 1] and should be discussed with the Medical Monitor)	4*
Immunomodulators/ Immunosuppressants [a]	Thalidomide or lenalidomide	4
	Calcineurin inhibitors: e.g., cyclosporine, voclosporin. Including topical use > 1 time per day (e.g.,pimecrolimus)	
	Topical calcineurin inhibitors applied more than one time per day	2
	Cyclophosphamide	12
	Plasmapheresis	
	Alkylating agents (not cyclophosphamide): e.g., chlorambucil	24
	Exceeding the maximum specified dose for antimalarials, methotrexate, 6-mercaptopurine, sulfasalazine, mycophenolate mofetil or sodium, azathioprine, dapsone, or retinoids	< 8
	JAK-STAT pathway inhibitors (e.g., tofacitinib)	24
Biologic therapies	Abatacept	12
	Intravenous Ig	
	Anti-TNFα: e.g., etanercept, adalimumab	
	Belimumab	16
	Anti-IFN: e.g., anifrolumab	24
	Anti-IL-6 receptor (tocilizumab, sarilumab) or anti-IL-6 (siltuximab)	

Medication type	Medications	Discontinuation (weeks) before the Screening Visit
	B cell depleting/modulating therapy such as anti-CD20 agents, telitacicept, atacicept, dual or other anti-B Lymphocyte Stimulator /proliferation inducing ligand neutralizing therapies	
	IL-12/IL-23 inhibitor: e.g., ustekinumab	
	Anti-IL-1 agents	
Vaccination [b]	Included but not limited to subunit or inactivated vaccines, and excluding SARS-CoV-2 vaccine or vaccine series (see Section 2.3.3)	2
	Live or live attenuated virus vaccine	4
Supplements (Herbal/nonherbal /Chinese medication)	Tryptophan	Screening
	Tripterygium, total glucosides of paeony	4
Antidepressants	Selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, St. John's wort, lithium.	3
	Fluoxetine	8
Anxiolytic	Buspirone	Screening
Analgesics	Tramadol, pethidine, fentanyl, dextromethorphan (e.g., in OTC cough remedies)	Screening
Antiemetics	Ondansetron, metoclopramide	Screening
Antibiotics	Linezolid, tedizolid	Screening
Investigational agents	BTK inhibitors: e.g., ibrutinib	Within the last 12 weeks or 5 half-lives, or as per washout requirement from the previous protocol, whichever is longest
Medications that prolong ECG QTc interval	Antipsychotics: haloperidol, ziprasidone, quetiapine, thioridazine, olanzapine, risperidone Antiarrhythmics: amiodarone, sotalol, dofetilide, procainamide, quinidine, flecainide Antibiotics: macrolides, fluoroquinolones Antidepressants: amitriptyline, imipramine, citalopram, amitriptyline Others: methadone, sumatriptan, ondansetron, cisapride	Consideration of substitute before study entry on a case-by-case basis; many of these also increase serotonin levels
Medications that are known to lower the seizure threshold	Anti-epileptic drugs, SSRIs, some analgesics(e.g., tramadol)	Screening
Other	Methylthioninium chloride (methylene75 blue)	Screening
Any medication administered during the study and related to an increase in CLE disease activity	(e.g., protein pump inhibitors, terbinafine).	During the study

a Use of more than 1 medication considered to have immunosuppressant or immunomodulatory properties as permitted by the protocol, not including antimalarials or CS, is not permitted.

b Vaccination for influenza virus and *S. pneumoniae* is allowed during Screening providing that vaccination completes 2 weeks before the Day 1 Visit.

AOX = aldehyde oxygenase, BTK = Bruton's tyrosine kinase, CLE = cutaneous lupus erythematosus, CS = Corticosteroids, ECG = electrocardiogram, IFN = interferon, Ig = immunoglobulin, IL = interleukin, JAK-STAT = Janus kinase/signal transducers and activators of transcription, NSAIDs = nonsteroidal anti-inflammatory drugs, OTC = over-the-counter, QTc = QT interval corrected for heart rate, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SSRI = selective serotonin reuptake inhibitors, TNFα = tumor necrosis factor alpha.

Table 7 Medications with Required Duration of Stable Dose

Medication type	Medications	Stable/unchanged dosage (weeks) before the Screening Visit
CS	≤ 30 mg prednisone-equivalent	2
	Topical corticosteroids Class I, II, III up to 2 times daily	4
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker		2
NSAIDs		2
Immunomodulators and/or immunosuppressants	Antimalarials: hydroxychloroquine (up to 400 mg/day), chloroquine (up to 500 mg/day)	8
	Dapsone (up to 100 mg/day) or retinoids (to discuss with Medical Monitor)	
	Sulfasalazine (up to 3 g/day)	
	Methotrexate (up to 25 mg/week)	
	Azathioprine (up to 2.5 mg/kg/day)	
	6-mercaptopurine (up to 1.5 mg/kg/day)	
	Mycophenolate mofetil or sodium (either as mycophenolate mofetil at up to 3 g/day or mycophenolate sodium up to 2,160 mg/day)	
	Leflunomide (up to 20 mg/day)	
Anticoagulation or antiplatelet therapy	Vitamin K antagonists Clopidogrel	4

CS = Corticosteroids, NSAIDs = nonsteroidal anti-inflammatory drugs.

Appendix 7 Corticosteroids Guidance

In order to demonstrate the potential CS-sparing effect of enpatoran and its treatment effect compared with placebo, CS must be tapered as clinically tolerated.

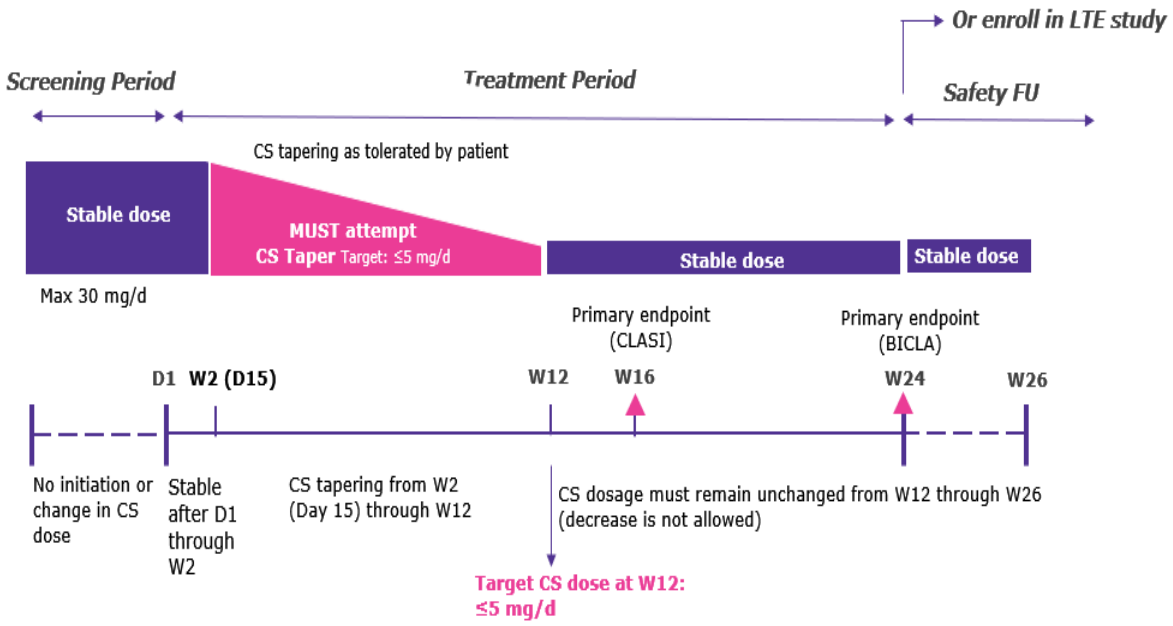
This guidance applies to Cohort A and Cohort B participants.

Table 8 Corticosteroid Guidance for the Screening period and 24-Week DBPC period

Time period/Other	CS rules and guidance	Outcome if rules not followed
Screening period (prior to Day 1)	CS dosage must remain unchanged. Maximum prednisone-equivalent daily dose is 30 mg.	Screening failure and participant could be rescreened.
Day 1 visit to Week 2	CS dosage must remain unchanged. Maximum prednisone-equivalent daily dose is 30 mg/day.	EAC may not necessarily adjudicate as non-responder.
Week 2 (starting on Day 15) to Week 12	MUST taper CS to a target prednisone-equivalent daily dose of ≤ 5 mg/day at Week 12 or earlier, as clinically tolerated (see Table 1 for protocol-specified CS tapering guidance)	
Week 12 to Week 24	CS dosage must remain unchanged (i.e., initiation, increase or decrease is not allowed) since changes in CS may affect the clinical endpoints (e.g., BICLA response, CLASI-A reduction, CS-sparing effect, etc.).	EAC will adjudicate as non-responder (note: does not apply to the safety follow-up period). Note: Classification as non-responder by the EAC has no impact on study procedures. The non-responders will continue on study treatment unless meeting criteria for treatment discontinuation (see Section 7).
Week 24 to Week 26 (Safety Follow-Up)	CS dosage must remain unchanged.	
CS rescue	Allowed only once after Day 1 through Week 8: up to prednisone-equivalent daily dose of 30 mg as rescue for worsening of SLE or CLE activity. The CS dose must be tapered within 7 days to ≤ CS dose used before the rescue (if not on any CS before the rescue, tapering within 10 days to prednisone-equivalent daily dose of 5 mg is allowed). Any CS increase after Week 8 for the treatment of worsening CLE or SLE is not permitted. Participants with CS increase for reasons other than treatment of worsening CLE or SLE may be classified as non-responders if determined by the EAC.	
Injectable Corticosteroids	Corticosteroids injected intramuscularly, intravenously, intra-articularly or SC are prohibited during the study (from the Screening Visit).	

CS = Corticosteroids, EAC = Endpoint Adjudication Committee.

Figure 3 **CS (prednisone-equivalent) dosing schedule**



BICLA = BILAG-based Combined Lupus Assessment, CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index, CS = Corticosteroids, FU = follow-up, LTE = Long-term extension, EAC = Endpoint Adjudication Committee.

Table 9 **Corticosteroid Tapering Guidance during the 24-Week DBPC period (example only)**

Investigators may choose to follow a tapering schedule different to the recommended guidance below due to different participant responses and tolerability of CS taper, but MUST reduce CS doses, as clinically tolerated, at every visit from Week 2 (~ Day 15) to Week 12 to reach and maintain a target dose of ≤ 5 mg/d at Week 12 or earlier. Participants starting with a prednisone-equivalent daily dose of ≤ 5 mg/d at Day 1 must not increase their daily dose above 5 mg of prednisone-equivalent.

Study week	Prednisone-equivalent daily dose (mg)						
0 (Day 1)	**30**	**25**	**20**	**15**	**12.5**	**10**	**7.5**
1	30	25	20	15	12.5	10	7.5
2	25	20	20	15	12.5	10	7.5
3	25	20	15	12.5	10	10	7.5
4	20	15	15	12.5	10	7.5	7.5
5	20	15	12.5	10	10	7.5	5
6	15	12.5	12.5	10	7.5	7.5	5
7	15	12.5	10	10	7.5	7.5	5
8	12.5	10	10	7.5	7.5	5	5
9	10	10	7.5	7.5	5	5	5
10	7.5	7.5	7.5	7.5	5	5	5
11	7.5	7.5	5	5	5	5	5
12	5	5	5	5	5	5	5

13 to 24	5	5	5	5	5	5	5
Study week	**Methylprednisolone-equivalent daily dose (mg)**						
0 (Day 1)	**24**	**20**	**18**	**16**	**12**	**10**	8
1	24	20	18	16	12	10	8
2	20	18	16	12	10	8	6
3	20	18	16	12	10	8	6
4	16	16	12	10	8	6	4
5	16	16	12	10	8	6	4
6	12	12	10	8	6	6	4
7	12	12	10	8	6	4	4
8	10	10	8	6	4	4	4
9	10	10	8	6	4	4	4
10	8	8	4	4	4	4	4
11	8	8	4	4	4	4	4
12	4	4	4	4	4	4	4
13 to 24	4	4	4	4	4	4	4

In Case of Failure to Taper CS

It is important to understand why CS are not tapered, especially in instances where participants seem to meet the criteria for taper (improving and/or maintaining an improvement of disease activity). It is acknowledged that on any given study visit, the CS taper is based on Investigator's clinical judgment of a participant's disease activity as well as their safety and well-being.

A CS dose decrease, or a series of decreasing doses, must be tapered for any participant whose disease is stable or improving from Week 2 (~ Day 15) to Week 12. The Investigator makes the final determination about whether tapering at a given time point is appropriate for a given patient. If tapering is initiated, the schedule will be collected on an eCRF. If tapering is not initiated, the Investigator will be required to explain the medical rationale for that. Either the Investigator or the Medical Monitor may initiate contact in order to clarify the rationale for tapering decisions.

The Medical Monitor and the EAC will review CS use and Medical Monitors will follow-up with the site for further discussions of all cases where there has been no decrease in CS dosing in participants who appear to be improving and/or maintaining an improvement of disease activity.

Table 10 Prednisone-equivalence Calculation (Total Daily Dose)

Medication	Equivalent (mg) to 1 mg of Prednisone
Betamethasone	0.15
Cortisone	5
Dexamethasone	0.15
Deflazacort	1.2
Hydrocortisone	4
Meprednisone	0.8
Methylprednisolone	0.8
Prednisolone	1
Triamcinolone	0.8

Non-systemic corticosteroids

From Screening to Week 24 of the DBPC treatment period, generally, there are no restrictions on non-systemic CS dosage (defined as optic, otic, intranasal, stable inhaled, and ophthalmic); For topical CS use, see Permitted medicines and prohibited medicines.

Topical Corticosteroids Class and Cross-reactivity

Topical corticosteroids Class I, II or III applicated for > 4 weeks, or > 2 times per day or topical corticosteroids Class IV are not allowed.

(adapted from Soost S, Worm M. Topical and Systemic Corticosteroids. Kanerva's Occupational Dermatology. 2012, 1035-43).

Table 11 Topical Corticosteroids Class

Agent by category (example)	Common concentration (%)
Class I: small effectiveness	
Hydrocortisone	0.5-1
Desoximetasone	0.05 cream, 0.25 ointment
Prednisolone	0.25-0.4
Class II: moderate effectiveness	
Flumethasone pivalate	0.02
Fluocinolone acetonide	0.025
Fluprednidene acetate	0.1-0.15
Hydrocortisone butyrate	0.1
Methylprednisolone aceponate	0.1
Prednicarbate	0.1
Triamcinolone acetonide	0.1 cream, 0.025 ointment
Class III: strong effectiveness	
Amcinonide	0.1
Betamethasone dipropionate	0.1 cream, 0.12 ointment
Betamethasone valerate	0.05-0.1
Diflucortolone valerate	0.1
Fluocinolone acetonide	0.025
Fluocortolone	0.25
Mometasone furoate	0.1
Class IV: very strong effectiveness	
Clobetasol propionate	0.05
Diflucortolone valerate	0.3

Appendix 8 Efficacy and Patient-Reported Outcome Assessments and Procedures

Refer to Table 1 for the study population and frequency for each assessment and procedure.

Columbia-Suicide Severity Rating Scale (C-SSRS)

Patients with SLE, especially those with neuropsychiatric manifestations, are at higher risk for suicide than expected. In a review of the medical records of 300 SLE patients over a 20-year period, 2% had a documented history of attempted suicide; one of them was fatal. All patients had a history of depression at the time of the suicide attempt (Karassa 2003).

The C-SSRS (Posner 2007) assesses the suicidal behavior and suicidal ideation in participants. Occurrence of suicidal behavior after randomization is defined as having answered "yes" to at least 1 of the 4 suicidal behavior subcategories (actual attempt, interrupted attempt, aborted attempt, and preparatory acts or behavior). Occurrence of suicidal ideation after randomization is defined as having answered "yes" to at least 1 of the suicidal ideation sub categories (wish to be dead, nonspecific 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).

Rationale

The C-SSRS is a low burden, tool designed to track suicidal AEs throughout any intervention study and is considered to be the "gold standard" for assessment. This scale is administered by the clinician or trained designee during the Screening Visit. The measure succinctly covers the full spectrum of suicidality addressing both behavior and ideation and is now strongly recommended by the US Food and Drug Administration in clinical studies. It is the prospective version of the Columbia-suicide classification system commissioned by the Food and Drug Administration, which provided the data for their safety analyses, and is used across numerous industry and National Institutes of Mental Health-sponsored studies.

Assessments

The C-SSRS is a unique and simple method of assessing both behavior and ideation that tracks all suicidal events and provides a summary of suicidality. It assesses the lethality of attempts and other features of ideation (frequency, duration, controllability, reasons for ideation and deterrents), all of which are significantly predictive of completed suicide.

The C-SSRS will be performed at the visits specified in Section 1.3. The trained rater will record the clinical observation on the scale which will be used as the source document.

Participants who answer "yes" to any suicidal behavior questions or to suicidal ideation questions 4 or 5 on the C-SSRS during the study should be referred for appropriate psychiatric care and the Medical Monitor notified.

Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)

The CLASI evaluates disease activity and damage in 2 separate scores. The activity scale includes measurements of erythema, scale, and hypertrophy, active alopecia, and mucous membrane disease, whereas the damage scale measure hyperpigmentation, atrophy, and scarring.

This distinction between activity and damage assures that the activity part of CLASI is responsive to short term therapy-induced changes while the damage indicators can examine accumulation of damage over time (Bonilla-Martinez ZL 2008). The CLASI is more reactive to therapy-induced changes of activity rather than remaining stable as the activity wanes and the chronic damage develops.

Scores range from 0 to 70 points for CLASI activity scale (CLASI-A) score. Mild, moderate, and severe disease corresponds with CLASI activity score ranges of 0 to 9, 10 to 20, and 21 to 70, respectively. It would be unusual to see a CLASI score of more than 30.

A copy of the CLASI form and glossary is provided in the Study Reference Manual.

Cutaneous Lupus Activity Investigator's Global Assessment (participants with CLASI-A ≥ 8 at Screening and Day 1 in Cohort A or B)

The CLA-IGA is a five point score that defines the level of disease severity based on overall lesion characteristics where 0 is "clear" and "4" is severe. Severity is determined by a combination of 3 plaque characteristics (erythema, scale, elevation) based on descriptions of each characteristic. Erythema is the primary characteristic that influences the rating, with plaque elevation, scaling and other secondary characteristics considered secondarily. Severity of the morphologic features are averaged over the burden of lesions.

Physician's Global Assessment of Cutaneous Lupus Disease Activity (participants with CLASI-A ≥ 8 at Screening and Day 1 in Cohort A or B)

The Physician's Global Assessment is used to quantify disease activity and is measured using an anchored visual analog scale (VAS). The Investigator will rate the overall disease activity status of the participant with respect to the lupus rash signs and symptoms of the participant, using a 100 mm VAS where 0 is "no cutaneous lupus disease activity" and 100 is "maximum cutaneous lupus disease activity".

Hybrid SELENA-SLEDAI

The hybrid SLE Disease Activity Index – Safety of Estrogens in Lupus Erythematosus National Assessment version (SELENA-SLEDAI) measures disease activity by recording features of active lupus as present or not present. The hybrid SELENA-SLEDAI is identical to the SELENA-SLEDAI except for the proteinuria definition that is the same as that in the SLEDAI-2K (Thanou 2019).

The hybrid SELENA-SLEDAI uses a weighted checklist to assign a numerical score based on the presence or absence of 24 signs or symptoms at the time of assessment or during the previous 30 days. Each symptom is assigned between one and eight points based on usual clinical importance, yielding a total score that ranges from 0 points (no symptoms) to a theoretical 105 points (presence of all defined symptoms). However, if scored correctly, it is rare for even the sickest patients to score more than 20 points.

A copy of the hybrid SELENA-SLEDAI and glossary is provided in the Study Reference Manual.

Physician's Global Assessment for SLE Disease Activity (All SLE participants in Cohort A or B)

The Physician's Global Assessment is used to quantify disease activity and is measured using an anchored visual analog scale (VAS). The Physician's Global Assessment will be determined on a continuous VAS that asks the Investigator to assess the participant's current disease activity anchors from 0 (no disease) to 3 (maximally severe disease), with the assessment made relative not to the participant's own most severe state but the most severe state possible in SLE per the Investigator's assessment. The Safety of Estrogens in Lupus Erythematosus National Assessment SLEDAI Physician's Global Assessment requires Investigators to compare the current visit to the previous visit in determining the score. Thus, they should look back at the last assessment and consider whether to move the mark to the right (patient worsening) or to the left (patient improving).

28-Joint Count

The swollen joint count reflects the number of joints with inflamed synovial tissue and the tender joint count is the number with tenderness on palpation. A 28-joint count includes metacarpophalangeal and proximal interphalangeal joints, wrists, elbows, shoulders and knees, and excludes the joints of the feet (Fuchs 1989). Since patients with SLE frequently present with joint pain and/or swelling (i.e., inflammatory arthritis), a 28-joint count form will be used in this Phase II clinical study to assess joint involvement. The number of swollen joints will be collected separately from the number of tender joints.

British Isles Lupus Assessment Group 2004

The BILAG 2004 Disease Activity Index (Yee 2010) evaluates SLE activity in a number of organ systems, based on the principle of "physician's intention-to-treat" (refer to Manual of Procedures). The primary purpose of the BILAG in this study is to assess possible worsening in specific organ systems. Additional analyses of improvements in disease activity as assessed by the BILAG 2004 will also be done.

A separate alphabetic score is assigned to each organ system, 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). Note that in the context of a CTP with medication restrictions and blinded IMP, the term "requiring" is not taken literally, but indicates that if all else were equal this would be the degree of treatment indicated. It is also understood that some participants respond to different levels of medication than others, so that in assessing participants with the BILAG "intent to treat" really means that most participants with this degree of symptom would require this level of treatment, not necessarily the participants in question
- 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.

All signs and symptoms scored must be due to SLE. Use of a glossary provided with the BILAG 2004 instrument and training of assessors in use of the instrument are essential to obtaining reliable and consistent results.

Requirements for BILAG-based Composite Lupus Assessment (BICLA) response are: (1) BILAG 2004 improvement (all A scores at Baseline improved to B/C/D, and all B scores improved to C or D); (2) no worsening in disease activity (no new BILAG 2004 A scores and ≤ 1 new B score); (3) no worsening of total SLEDAI score from Baseline; (4) no significant deterioration (< 10% worsening) in visual analog PGA and (5) no treatment failure (defined as non-protocol treatment, i.e., protocol-prohibited medications as confirmed by EAC (i.e., new or increased immunosuppressives or antimalarials, corticosteroid use not compliant with protocol rules), or premature discontinuation from study treatment) (Wallace 2014).

BILAG Flare

Use of the BILAG index for evaluating flares has been identified as a meaningful way of evaluating the efficacy of drugs; this judgment has been corroborated by external advisors and regulatory authorities.

BILAG assessments should be conducted by a trained evaluator.

The BILAG index flare definition were used in the SLICC Flare study in May 2009 published in Annals of Rheumatic Diseases (Isenberg 2011).

On the participant level:

1. 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 patient's condition during the previous month

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

3. A mild flare is defined as one single BILAG B score in any organ systems due to items that are new or worse* in the month leading up to the current visit, compared to previous month, or at least three BILAG C scores in any organ systems due to items that are new or worse

4. No flare is defined as without meeting any of these criteria.

*On the organ system level:

Investigators will be trained to score worse only if there is significant deterioration compared to the prior month and to score new only when the item was not present in the prior month according to the BILAG glossary. In organs (Renal and Hematological) in which an A, B, or C score depend on whether or not laboratory results are attributed to SLE, Investigators will be queried to ensure that there is medical justification for this decision.

A copy of the BILAG 2004 and glossary is provided in the Manual of Operations.

Systemic Lupus International Collaborating Clinics / American College of Rheumatology Damage Index

The SLICC/ACR Damage Index evaluates cumulative damage in SLE (Gladman 1996). These changes may or may not be related to SLE. In order to ensure that features are not reversible components of active inflammation, most items are scored only if they have been present for at least six months. Scores range from 0 to 47 points, with higher scores indicating greater cumulative damage. However, it would be exceedingly rare to see a damage index score of greater than 5 and most participants in clinical studies have scores ranging from 0 to 2.

Further information on the SLICC/ACR Damage Index is provided in the Manual of Procedures.

SLEDAI Flare Index

The SFI can be used with any version of the SLEDAI, and will be used with the hybrid SELENA-SLEDAI for the purposes of this trial.

A mild/moderate flare is defined as any of the following:

- Increase in SLEDAI instrument score of 3 points or more (but total score not to more than 12).
- New or worse discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus; or nasopharyngeal ulcers; or pleuritic; or pericarditis; or arthritis; or fever due to SLE.
- Increase in prednisone, but not to > 0.5 mg/kg/day.
- Added NSAID or hydroxychloroquine (or chloroquine) for SLE activity.
- ≥ 1.0 increase in PGA score, but score not to exceed 2.5 (assuming the PGA score has been transformed to a 0-3 point scale).

A severe flare is defined as any of the following:

- Increase in SLEDAI instrument score leading to total score > 12.
- New or worse central nervous system SLE; or vasculitis; or nephritis; or myositis; or platelets < 60,000/mm^3, or hemolytic anemia with hemoglobin < 70 g/L or decrease in hemoglobin > 30 g/L AND requiring: double prednisone, or prednisone increase to > 0.5 mg/kg/day, or hospitalization due to SLE.
- Increase in prednisone to > 0.5 mg/kg/day.
- New cyclophosphamide, azathioprine, methotrexate, or mycophenolate for SLE activity.
- Hospitalization for SLE activity.
- Increase in PGA score > 2.5 (assuming the PGA score has been transformed to a 0-3 point scale).

The hybrid SELENA-SLEDAI and SFI assessments must be conducted by a trained evaluator.

A copy of the hybrid SELENA-SLEDAI form is provided in a separate Manual of Procedures.

Montreal Cognitive Assessment (MoCA)

The Montreal Cognitive Assessment (MoCA) is designed as a rapid screening instrument for mild cognitive dysfunction. The MoCA is highly effective for detecting cognitive impairment in SLE patients (Paez-Venegas 2019). It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. The MoCA may be administered by anyone who understands and follows the instructions, however, only a health professional with expertise in the cognitive field may interpret the results. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal.

Patient-Reported Assessments

Functional Assessment of Chronic Illness Therapy-Fatigue

The FACIT-Fatigue is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function (Wolfe 1996). It uses a 5-point Likert-type scale (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; 4 = very much). As each of the 13 items of the FACIT-Fatigue scale ranges from 0–4, the range of possible scores is 0-52, with 0 being the worst possible score and 52 the best. To obtain the 0-52 score, each negatively worded item response is recoded so that 0 is a bad response and 4 is good response. All responses are added with equal weight to obtain the total score. Fatigue is among the most prevalent symptoms of SLE, and can have profound effects on subjects' HRQoL (Wolfe 1996; Yellen 1997). The FACIT-Fatigue has been validated in subjects with SLE being a valid and responsive measure of fatigue in subjects with SLE (Hewlett 2005; Kosinski 2013; Lai 2011; Strand 2015) and will also be evaluated in CLE subjects.

Medical Outcome Study (MOS) Sleep Scale

The MOS Sleep scale is a 12-item self-reported measure of sleep quality, developed for use across different chronic conditions (Hays 1992; Hays 2005). The measure addresses multiple domains of sleep quality, including initiation, maintenance, respiratory problems, quantity, perceived adequacy and somnolence (Hays 1992; Hays 2005). Subscale scores are generated for each of the domains, with higher scores indicating greater sleep disturbance.

This scale will be completed by all study participants (i.e., SLE or CLE) at relevant/respective study visits.

Patient Experience In-trial Qualitative Interviews

Patient experience in-trial qualitative interviews will be performed as part of the clinical trial, to document the experience of treatment from the patient perspective and to understand the impact of enpatoran in the treatment of lupus. Specifically, the interviews are expected to capture 1) the patient experience of treatment in the clinical study, 2) the patient experience of changes (or no change) in symptoms and the ability to function or perform activities that are important to the patient, and 3) the patient perspective on the meaningfulness and importance of score change in PRO assessments.

The interviews will follow a one-on-one format and will conducted via telephone, based on a semi-structured interview guide. Each interview will be approximately 60 minutes and will be completed within 2 weeks of the participant's completion of the EOT or ET visit for the DBPC period of the study.

The interviews will be offered to all participants from a subset of sites from selected countries participating in the clinical study. Participants from the selected sites will be provided with a description of the qualitative interview and will be invited to participate. Details about the qualitative interviews will be included in the clinical trial informed consent form and ethics and IRB review submissions.

All interviews will be conducted by experienced moderators and will be audio recorded. The content of the interview will be transcribed, and the audio recording will be destroyed to protect participant privacy. All personal information will be removed from the transcripts. Using the interview transcripts, dominant trends will be identified in each interview and then compared across the results of the other interviews to generate themes or patterns in the way participants describe their treatment and clinical trial experiences as well as their perceptions of treatment benefit and meaningful change in PRO measure scores over the trial period.

Should an interviewer become aware of any potential adverse event during the telephone interview, the interviewer will share the relevant information with the participant's clinical site staff within 24 hours. The clinical site will be responsible for follow-up with the participants and the site's principal investigator will be responsible for determining the clinical significance of the event.

Lupus Symptom Severity Diary

The Lupus SSD was developed as a self-reported measure of SLE symptoms and covers key symptoms important for people with SLE (Mathias 2018). Each symptom is assessed on an 11-point numeric rating scale, i.e., from a score of 0 (absent/did not have) to 10 (worst imaginable). Study participants with active SLE will be asked to complete the Lupus SSD on relevant/respective study visits. Data generated from the trial will support further validation of this instrument.

This scale will be completed by study participants with SLE in Cohort B at relevant/respective study visits.

PROMIS SF v2.0 – Physical Function 10a

The PROMIS SF v2.0 – Physical Function 10a [PROMIS Physical Function10a] was developed as a self-reported measure of physical function (i.e. for assessing current capability to perform physical activities), for use in the general population and adults with chronic health conditions (Cella 2010; Schalet 2016).

The PROMIS Physical Function10a is scored on a T-score metric using item response theory (IRT) "response pattern scoring" methods based on responses on all 10 items of the short form. The T-score metric is referenced to the US general population, has a mean of 50 and a standard deviation (SD) of 10, with higher scores indicating better physical function. For example, a T-score of 40 would be one SD below the US general population.

Study participants with **SLE in Cohort B** will be asked to complete the PROMIS Physical Function10a on relevant/respective study visits.

Patient Global Assessment of Lupus Symptoms (PtGA)

The PtGA is a single item scale assessing the **severity of lupus symptoms** in the past 7 days. Responses are captured on a 5-point Likert scale (i.e., from "none" to "very severe"). Global questions capturing the current state of disease severity are broadly recommended by the FDA as anchors when evaluating clinically important change in which the judgment of meaningful change is made by the subject (Amirfeyz 2009).

This scale will be completed by study participants with SLE in Cohort B at relevant/respective study visits.

Patient Global Impression of Change in Lupus Symptoms (PGIC)

The PGIC is a self-rated scale that asks respondents to describe the retrospective **change in their lupus symptoms** at a given time point. Responses are captured on a 7-point scale, as follows: 1 (much better), 2 (moderately better), 3 (a little better), 4 (no change), 5 (a little worse), 6 (moderately worse) and 7 (much worse) (Hurst 2004).

Study participants will be asked to select the response (i.e. score) that matches their degree of change at the respective study visits, since starting to take study medication. The PGIC is useful as an anchor when assessing clinically important change in which the judgment of meaningful change is made by the participant (Amirfeyz 2009).

This scale will be completed by study participants with SLE in Cohort B only, on relevant/respective study visits.

Patient Global Assessment of Lupus Skin Symptoms (Skin PtGA)

The Skin PtGA is a single item scale assessing the **severity of lupus skin symptoms** in the past 7 days. Responses are captured on a 5-point Likert scale (i.e., from "none" to "very severe").

This scale will be completed by study participants with SCLE, DLE or SLE with active skin rash (CLASI-A ≥ 8 at Screening and Day 1 in Cohort A or B) only.

Patient Global Impression of Change in Lupus Skin Symptoms (Skin PGIC)

The skin PGIC is a self-rated scale that asks respondents to describe the retrospective **change in their lupus skin symptoms** at a given time point. Responses are captured on a 7-point scale, as follows: 1 (much better), 2 (moderately better), 3 (a little better), 4 (no change), 5 (a little worse), 6 (moderately worse) and 7 (much worse) (Hurst 2004).

This scale will be completed by study participants with SCLE, DLE or SLE with active skin rash (CLASI-A ≥ 8 at Screening and Day 1 in Cohort A or B) only, on relevant/respective study visits.

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, designed for use across dermatologic conditions, and three additional items specific for lupus (Ogunsanya 2019; Chren 1996).

Subscale scores are generated for each of the three original domains of the Skindex-29 i.e., symptoms, functioning, and emotional well-being. In addition, a photosensitivity subscale score is calculated based on two of the additional lupus-specific items related to photosensitivity (Foering 2012). For all subscale scores, higher scores indicate lower functioning/worse symptoms.

This scale will be completed by study participants with SCLE, DLE or SLE with active skin rash (CLASI-A ≥ 8 at Screening and Day 1 in Cohort A or B) only.

Itch Numeric Rating Scale (NRS)

The Itch NRS is a self-rated single item scale designed for assessing worst itch in the past 7 days. The scale utilizes an 11-point Numeric Rating Scale (NRS), scored from of 0 (no itch) to 10 (worst imaginable itch).

This scale will be completed by study participants with SCLE, DLE or SLE with active skin rash (CLASI-A ≥ 8 at Screening and Day 1 in Cohort A or B) only.

Appendix 9 Pharmacogenetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact study intervention absorption, distribution, metabolism, and excretion; mechanism of action of the study intervention; disease etiology; and/or molecular subtype of the disease being treated.
- In addition, DNA samples may be used for research related to safety endpoints, PK, PD, disease activity, or lupus and related diseases. They may also be used to develop tests or assays, including diagnostic tests related to safety endpoints, PK, PD, disease activity, or lupus and related diseases. Pharmacogenetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- The results of pharmacogenomics analyses may be reported in the CSR or in a separate study summary.
- Details on processes for collection and shipment of these samples can be found in the Laboratory Manual. The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- Retention time and possible analysis of DNA sample after the study ends are specified in the respective ICF.

Appendix 10 Sponsor Signature Page

Study Title:	A Phase II, 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
Regulatory Agency Identifying Numbers:	IND: 145565 EudraCT: 2021-004648-27
Clinical Study Protocol Version:	1.0/ 28 September 2021

I approve the design of the clinical study:

Sanjeev Roy — Signature

29-Sep-2021 — Date of Signature

Name, academic degree:	Sanjeev Roy, MD
Function/Title:	Medical Responsible
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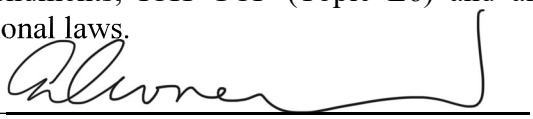
General Merck Phone Number:	+41 795984857
General Merck Fax Number:	Not Applicable

Appendix 11 Coordinating Investigator Signature Page

Study Title:	A Phase II, 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
Regulatory Agency Identifying Numbers:	IND: 145565 EudraCT: 2021-004648-27
Clinical Study Protocol Version:	1.0/ 28 September 2021
Site Number:	

I approve the design of the clinical study, am responsible for the conduct of the study at this site and understand and will conduct it per the clinical study protocol, any approved protocol amendments, ICH GCP (Topic E6) and all applicable Health Authority requirements and national laws.



29/9/21

Signature Date of Signature

Name, academic degree:	Eric Francis Morand, MBBS, PhD, FRACP
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Appendix 12 Principal Investigator Signature Page

Study Title:	A Phase II, 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
Regulatory Agency Identifying Numbers:	IND: 145565 EudraCT: 2021-004648-27
Clinical Study Protocol Version:	1.0/ 28 September 2021
Site Number:	

I am responsible for the conduct of the study at this site and understand and will conduct it per the clinical study protocol, any approved protocol amendments, ICH GCP (Topic E6) and all applicable Health Authority requirements and national laws.

I also understand that Health Authorities may require the Sponsors of clinical studies to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for complying with the regulatory requirements. Therefore, I agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

_____ _____

Signature Date of Signature

Name, academic degree:

Function/Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address: