Clinical Study Protocol

Phase 2a, Randomized, Double-blind, Placebo-controlled Trial of PRV-3279 EVAluation In Lupus (PREVAIL-2)

Protocol Number: **PRV-3279-2a**

Compound: **PRV-3279**

Study Phase: **2a**

Short Title: **PRV-3279-2a trial in systemic lupus**

Acronym: **PREVAIL-2**

Sponsor Name: **Provention Bio, Inc.**
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Regulatory Agency Identifier Number(s): IND: 121930

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Date

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Summary of Changes

Protocol version 1.1 dated 20Aug2021 to 2.0 dated 16Dec2022

Protocol PRV-3279-2a version 1.1 dated 20Aug2021 has been amended to version 2.0 dated 16Dec2022. Substantive changes to the previous version of the protocol are listed in the table below along with rationales. In addition, minor corrections and administrative/editorial changes and clarifications have been made throughout the document. All changes are clearly identified in the track-changes version of the amendment.

Section	Rationale for Change	Original Text	Revised Text
Throughout the protocol	China and the option for geographies in addition to Hong Kong and the US have been included in the PREVAIL-2 study		
	For enhanced safety, urinalysis has been included in all study visits		
	The option of a serum pregnancy test has been added to all treatment visits.		
	Text clarifying that covid tests must demonstrate negative results prior to administering study drug has been added		
	[redacted]		

Section	Rationale for Change	Original Text	Revised Text
Title Page	The sponsor signatory has been changed	[redacted]	[redacted]
1.3. Schedule of Activities, 8.5. Pharmacokinetic Assessments	Additional PK sampling timepoints have been reduced for patient and site convenience and windows have been added to each timepoint	Additional samples will be collected at the Day 1 and Day [redacted] visits, at the following timepoints: [redacted]	Additional samples will be collected at the Day 1 and Day [redacted] visits, at the following timepoints: [redacted].
1.3. Schedule of Activities	Receptor Occupancy sampling timepoints have been reduced for patient and site convenience and windows have been added to each timepoint	Additional samples will be collected at the Day 1 and Day [redacted] visits, at the following timepoints: [redacted]	[redacted]e.
1.3. Schedule of Activities, 8.1.1. Screening Procedures, 8.2.2. Vital Signs	Appropriate patient position and assessment window for obtaining vital signs have been defined	On dosing days, vital signs should be performed before the study drug infusion and approximately 30 minutes after the end of infusion.	On dosing days, vital signs should be performed <u>after patient is supine for at least 5 minutes during the 30 minutes</u> before the study drug infusion and approximately 30 minutes after the end of infusion.
2.5. Risk-Benefit Assessment, 4.1. Design,	[redacted]	The study population will not be restricted to these patients, but, using a rapid gene expression profiling system (e.g., DxTerity or similar) at Screening, a reasonably accurate surrogate for the presence or absence of this, or part of this	[redacted]

Section	Rationale for Change	Original Text	Revised Text
		phenotype will be one of the stratification factors during randomization.	[redacted]
4.1 Design	The option for extending the screening period by two weeks at the discretion of the Medical Monitor has been added to allow flexibility for delays due to sample analysis delays or other delayed screening results	If a patient takes any new SLE medications (other than NSAIDs), increases the dose of current SLE medications (other than NSAIDs), misses 2 consecutive doses or 3 or more total doses of the study drug, the patient should permanently discontinue study drug and continue study procedures and assessments, but will be documented as a nonresponder in the primary and applicable secondary efficacy endpoints.	If a patient takes any new SLE medications (other than NSAIDs), increases the dose of current SLE medications (other than NSAIDs), misses 2 consecutive doses or 3 or more total doses of the study drug, the site should contact the Medical Monitor to discuss permanent discontinuation of the study drug. The patient will be encouraged to continue study procedures and assessments, but will be documented as a nonresponder in the primary and applicable secondary efficacy endpoints.
5.2 Exclusion Criteria, 6.6.1.1. Prohibited Medications at Entry	Clarification for exclusion criterion 1 regarding excluded SLE medications at randomization has been added	1. Currently receiving disease-modifying antirheumatic drug (DMARD), JAK inhibitor, or calcineurin inhibitor treatment for induction or maintenance treatment of nephritis or any other reason.	1. Currently receiving induction treatment or maintenance treatment (e.g., mycophenolate mofetil, azathioprine, JAK inhibitor, calcineurin inhibitor, others) for lupus nephritis.
5.2 Exclusion Criteria	Clarification of eligibility criteria for CBC and requirements for repeat samples to determine eligibility	7. Complete blood count (CBC): a. white blood cell (WBC) count <1.5×109/L;	7. Complete blood count (CBC): a. white blood cell (WBC) count <1.5×109/L;

Section	Rationale for Change	Original Text	Revised Text
		b. lymphocyte count <0.3×109/L; c. neutrophil count <1.0×109/L; d. hemoglobin ≤8.0 g/dL; e. platelet count <40×109/L. (If the platelet count is <70× 109/L, a repeat sample must not decrease >5×109 /L within the Screening period. If lymphocyte count is <0.5×109/L, a repeat sample must not be decreasing.)	b.lymphocyte count <0.3×109/L (If lymphocyte count is <0.5×109/L, a repeat sample must be collected and analyzed and must not be decreasing.); c.neutrophil count <1.0×109/L; d.hemoglobin ≤8.0 g/dL; e.platelet count <40×109/L (If the platelet count is <70× 109/L, a repeat sample must be collected and analyzed and must not decrease >5×109 /L within the Screening period.)
5.2 Exclusion Criteria, 6.6.1.2. Prohibited Medications at Any Time During the Study	Clarification for exclusion criterion 13 regarding vaccinations has been added	13. Received a live attenuated vaccine within 2 months of Screening, received a non-live or mRNA vaccine within 2 weeks of Screening, or expecting to receive any vaccine during the study period.	13. Received a live attenuated vaccine within 2 months of Screening, or received a non-live or mRNA vaccine within 2 weeks of Screening. Patients should be advised to delay vaccines until after the study completion to ensure optimal vaccine efficacy; however receipt of a non-live vaccine after randomization is not exclusionary.
5.2 Exclusion Criteria	Clarification for exclusion criterion 14 regarding patients with positive QuantiFERON TB-	QuantiFERON TB-Gold-positive patients are allowed to participate in the study if chest x-ray confirms	QuantiFERON TB-Gold-positive patients may be allowed to participate in the study if all the following are

Section	Rationale for Change	Original Text	Revised Text
	Gold results has been added	no active disease, and one of the following conditions is met: − Active TB is ruled out by a certified TB specialist or pulmonologist who is familiar with diagnosing and treating TB (as acceptable per local practice). − The patient has documented evidence of satisfactory completion of LTBI-appropriate prophylaxis as per WHO or national guidelines within the last 5 years following review by a physician specializing in TB. − The patient has completed at least 4 weeks of LTBI-appropriate prophylaxis prior to randomization with agents recommended as preventative therapy for LTBI according to country-specific/Centers for Disease Control and Prevention (CDC) guidelines and is willing to complete the entire course of recommended LTBI therapy.	true: (a) chest x-ray confirms no active disease, and (b) the patient has completed at least 4 weeks of LTBI-appropriate prophylaxis prior to randomization with agents recommended as preventative therapy for LTBI according to country-specific/Centers for Disease Control and Prevention (CDC) guidelines and is willing to complete the entire course of recommended LTBI therapy, and (3) the CAC confirms the patient to be stable for inclusion.
Table 1 Treatment Interruption	Corrections made to levels required at screening and for	No return Screening level	No return to level required at Screening

Section	Rationale for Change	Original Text	Revised Text
Based on Safety Laboratory Tests	treatment interruptions; conditions for next dose suspended clarified		
8. Study Assessments and Procedures	Corrections and clarifications made to amount of blood collected	The maximum amount of blood collected from most patients over the duration of the study will not exceed 500 mL. Due to additional PK blood sample collections (Section 8.5), the maximum blood volume will be approximately 550 mL in approximately 20 patients at Hong Kong sites (and other select patients).	The maximum amount of blood collected from most patients over the duration of the study will not exceed 525 mL. Due to additional PK blood sample collections (Section 8.5) and Receptor Occupancy sample collections (Section 8.7), the maximum blood volume will be approximately 630 mL in approximately 30 patients.
8.1 Study Procedures	New text added to clarify timing of PRO questionnaires at study visits		Patients will complete PRO questionnaires prior to any blood draws or other interventions with the study staff.
8.1.2. Baseline/ Randomization Visit (Week 0, Day 1)	Additional text added to clarify requirements and timing for confirming patient eligibility at randomization visit	Upon arrival at the clinic, patients will complete the PRO questionnaires prior to any blood draws or other interventions with the study staff. Patients will then have an interim history and a brief physical examination performed (including body weight). The Investigator must confirm that there has been "definite improvement" or	Upon arrival at the clinic, patients will complete the PRO questionnaires prior to any blood draws or other interventions with the study staff. Patients will then have an interim history and a brief physical examination performed (including body weight). The Investigator will also complete the hSLEDAI, ssPGA, SFI, mSFI, BILAG, CLASI,

Section	Rationale for Change	Original Text	Revised Text
		"major or complete improvement" using the CGIC. The Investigator will also complete the hSLEDAI, ssPGA, SFI, mSFI, BILAG, CLASI, and joint counts. A pre-dose urinalysis (with reflex protein/creatinine ratio if dipstick is ≥2+) and urine pregnancy test (for WOCBP) will be obtained. Vital signs, ECG, AE, and concomitant medication assessments will be performed. Rapid COVID-19 test will be performed locally.	and joint counts. To assess eligibility, the Investigator must confirm that the patient has achieved at least a moderate improvement in SLE signs and symptoms as indicated by: CGIC score of "definite improvement" or "major or complete improvement" **AND** ≥4-point decrease in hSLEDAI score from Screening, **OR** improvement by ≥1 severity grade in at least one BILAG system that was severe (A score) or moderate (B score) at Screening (i.e., from A to B-D or from B to C or D). A pre-dose urinalysis and urine or serum pregnancy test (for WOCBP) will be obtained. Vital signs, ECG, AE, and concomitant medication assessments will be performed. Rapid COVID-19 test will be performed locally to confirm negative result prior to study drug administration.
10.2. Appendix 2: Clinical	Corrections made to chemistry analysis	Chemistry: sodium, potassium, chloride,	Chemistry: sodium, potassium, chloride,

Section	Rationale for Change	Original Text	Revised Text
Laboratory Tests		calcium, ALP, ALT, AST, BUN, creatinine, total protein, albumin, glucose, phosphorous, and bicarbonate	calcium, ALP, ALT, AST, BUN, creatinine, CPK, direct and total bilirubin, total protein, albumin, glucose, phosphorous, and bicarbonate
Note that all protocol changes were also reflected in Section 1.1 Synopsis			

1. Protocol Summary

1.1. Synopsis

Protocol Title: Phase 2a, Randomized, Double-blind, Placebo-controlled Trial of PRV-3279 EVAluation In Lupus (PREVAIL-2)

Short Title: PRV-3279-2a trial in systemic lupus

Rationale: PRV-3279 is a humanized dual affinity re-targeting (DART®) protein that binds to both CD32B (Fcγ receptor IIb) and CD79B on B cells only. The mechanism of action and early clinical data suggest that PRV-3279 may be a safe and effective treatment for chronic systemic lupus erythematosus (SLE).

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To evaluate the ability of PRV-3279 to prevent flare, i.e., to maintain the improvement in SLE signs and symptoms for 24 weeks, after the amelioration of active disease induced by corticosteroid treatment before Day 1 with the withdrawal of major background medications.	Proportion of patients who maintain the improvement in SLE disease activity from Baseline (Day 1) to Week 24, defined as no lupus flare during this period. A lupus flare is defined as: • Investigator's assessment that the SLE activity meets the Lupus Foundation of America (LFA) international consensus definition for a flare[1] **AND** • A score of "definite worsening" or "severe worsening" on Clinician's Global Impression of Change (CGIC), **AND** • at least one of the following occurrences: o an increase of ≥4 points from baseline in the hybrid Safety of Estrogens in Lupus Erythematosus National Assessment -Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score (hSLEDAI), **OR** o ≥1 organ with an A score (severe) or B Score (moderate) item rated new or worse on British Isles Lupus Assessment Group (BILAG) Index

Objectives	Endpoints
Secondary	
Efficacy: 1. To evaluate whether PRV-3279 prolongs the duration of disease amelioration induced by corticosteroids before Day 1.	1. Time to treatment failure. Treatment failure is defined compared to Baseline (Day 1): • Occurrence of an SLE flare (as defined in the primary endpoint), **OR** • Missing 2 consecutive doses or 3 or more total doses of the study drug for any reason, **OR** • Initiation of a new SLE medication, **OR** • Increased dose of current SLE medication, with the exception of nonsteroidal anti-inflammatory drugs (NSAIDs), **OR** • Patient withdrawal from the study before the Week 24 visit
2. To determine whether PRV-3279 allows patients to achieve and sustain European League Against Rheumatism (EULAR)-recommended treatment goal of low disease.	2. Proportion of patients who meet either of the following criteria at Week 24: • hSLEDAI score <3 **OR** • All BILAG scores are C or less
3. To evaluate the effect of PRV-3279 on patient-reported physical functioning.	3. Change from Screening to Week 24 in the Physical Component Score (PCS) score in the Short Form 36 Health Survey (SF-36).
4. To determine whether PRV-3279 can reduce one or more signs and symptoms of SLE using a stringent definition for improvement in each sign or symptom, based on the SLE Responder Index-4 (SRI-4)	4. Proportion of patients who meet the criteria for SRI-4 at Week 24 compared to Screening. SRI-4 is defined as: • A hSLEDAI score decrease of ≥4 points, **AND** • No new organs with a BILAG A (severe) score, **AND** • No more than 1 new organ with a BILAG B (moderate) score, **AND**

Objectives	Endpoints
5. To determine whether PRV-3279 reduces disease activity in all organs that are rated as moderately or severely active at Screening using the BILAG Index.	• No SELENA-SLEDAI Physician's Global Assessment (ssPGA) score increase of >0.3 points. 5. Proportion of patients who meet the BILAG-based Combined Lupus Assessment (BICLA) criteria at Week 24 compared to Screening: • Reduction by ≥1 grade in all organs with BILAG A or B scores **AND** • No worsening of SLEDAI or other BILAG organs **AND** • No ssPGA score increase of ≥0.3 points.
Safety: To evaluate the safety and tolerability of PRV-3279.	Frequency of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), TEAEs leading to drug withdrawal, adverse events of special interest (AESIs), and total serum immunoglobulin levels. Frequency of potentially clinically important changes in clinical laboratory tests, vital signs, electrocardiograms (ECGs), and physical examinations.
PK and Immunogenicity: To evaluate the pharmacokinetics (PK) and immunogenicity of PRV-3279 in patients with SLE.	Serum concentrations of PRV-3279. Anti-drug antibody (ADA) titers.
Exploratory	
1 [redacted]	[redacted]

1. "A flare is a measurable increase in disease activity in one or more organ systems involving new or worse clinical signs and symptoms and/or laboratory measurements. It must be considered clinically significant by

Objectives	Endpoints

the assessor, and usually, there would be at least consideration of a change or an increase in treatment." (Ruperto 2011)

Design

This is a randomized, double-blind, placebo-controlled study in adult patients with active SLE. Approximately 100 eligible patients will be randomized at a 1:1 ratio to receive treatment with either 10 mg/kg PRV-3279 or placebo. The study drug, PRV-3279 or placebo, will be given as an intravenous (IV) infusion over 2 hours, every 4 weeks from Week 0 through Week 20 for a total of 6 doses. Two follow-up visits are planned (Week 24 and Week 28). The EOS visit will occur at Week 28.

During the Screening period, the patient will receive an intramuscular (IM) injection of methylprednisolone acetate (Depo-Medrol® or equivalent) at a dose of ≥40 mg to induce improvement of SLE signs and symptoms. Repeat injections may be given to further ameliorate symptoms, up to a total of 4 injections with a maximum total dose of 320 mg.

Starting on Day 1 (Baseline/Randomization visit) and continuing throughout the study, the only background SLE treatments that may be continued are hydroxychloroquine up to 400 mg per day (or other antimalarial [Section 10.5]), up to 10 mg per day prednisone (or equivalent corticosteroid [Section 10.5]), and NSAIDs. Patients will be asked to abstain from NSAIDs on the mornings of the Randomization visit and all subsequent study visits (NSAIDs can be re-started after completing all evaluations on the day of each study visit). On other days throughout the study, NSAIDs are allowed without restrictions. All other SLE treatments taken at the time of Screening will be withdrawn during the Screening period and prior to Randomization.

Potentially eligible patients will return to the study site to confirm eligibility for randomization on Day 1. The Investigator must confirm that the patient has achieved at least a moderate improvement in SLE signs and symptoms as indicated by:

CGIC score of "definite improvement" or "major or complete improvement"

AND

≥4-point decrease in hSLEDAI score from Screening, **OR** improvement by ≥1 severity grade in at least one BILAG system that was severe (A score) or moderate (B score) at Screening (i.e., from A to B-D or from B to C or D).

Note: Assessments by hSLEDAI and BILAG Index at the Randomization visit may not follow the standard 4-week assessment rules but will be scored by a simple clinical comparison of SLE disease activity at Week 0 (Day 1, Randomization Visit) to the Screening Visit.

If the patient is confirmed eligible, randomization will occur through an interactive voice/web response system (IVRS/IWRS) and will be stratified by the presence or absence of serum anti-double-stranded deoxyribonucleic acid (anti-dsDNA) antibodies. [redacted]

At each visit, formal assessments of disease activity and safety will be conducted, and laboratory specimens will be collected. Patients will receive IV infusions of the study drug every 4 weeks from Week 0 through Week 20, inclusive.

All efforts should be made to retain all patients in the study, regardless of their compliance with study procedures. If a patient takes any new SLE medications (other than NSAIDs), increases the dose of current SLE medications (other than NSAIDs), misses 2 consecutive doses or 3 or more total doses of the study drug, then the site should contact the Medical Monitor to discuss whether permanent discontinuation of the study drug is necessary. Patients who permanently discontinue study drug will be encouraged to continue study procedures and assessments, but will be documented as a nonresponder in the primary and applicable secondary efficacy endpoints. In the case of medications taken briefly and in error, exception may be considered following discussion with, and approval of, the Medical Monitor.

If a lupus flare occurs (as defined in the primary endpoint [Section 1.1 and Section 3]), the patient should contact the study site immediately and be seen as soon as possible for a Flare Assessment visit, regardless of visit schedule, and should be assessed according to the Schedule of Activities (SoA, Section 1.3). SLE medications may be prescribed as warranted to control the symptoms and/or signs present at this visit. If confirmed, the patient will discontinue any further study drug administration and will be considered a nonresponder in the primary and applicable secondary efficacy endpoints.

Throughout the study, SLE disease activity and patient -reported outcomes (PROs) will be assessed using the following instruments:

- Disease Activity Instruments:
  - The hybrid Safety of Estrogens in Lupus National Assessment Systemic Erythematosus Lupus Erythematosus Disease Activity Index [hSLEDAI]
  - The SELENA-SLEDAI Physician's Global Assessment (ssPGA)
  - SELENA-SLEDAI Flare Index (SFI)
  - Modified SELENA-SLEDAI Flare Index (mSFI)
  - British Isles Lupus Assessment Group (BILAG) Index
  - Clinician's Global Impression of Change (CGIC)
  - Cutaneous Lupus Erythematous Disease Area and Severity Index (CLASI)
  - Tender and swollen joint counts
- PROs:
  - Short Form 36 Health Survey (SF-36)
  - Patient Global Impression of Change in Clinical Status (PGIC)
  - Patient Global Impression of Change in Disease Severity (PGIS)
  - Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue Scale)

Safety assessments will include TEAEs, vital signs, physical examination findings, 12-lead ECGs, and clinical laboratory tests (hematology, chemistry, urinalysis, coagulation panel, lupus-related serologies, SLE disease activity markers, and T cell, B cell, natural killer cell [TBNK] panel). A rapid COVID-19 test will be performed at Screening and must be confirmed to be negative prior to each study drug administration. A urine or serum pregnancy test will be

performed for women of childbearing potential (WOCBP) onsite prior to each study drug administration (serum pregnancy test at Screening).

PK (serum PRV-3279 concentrations), PD (biomarkers), and immunogenicity assessments will also be conducted.

Disclosure Statement: This is a Phase 2a, double-blind, placebo-controlled trial with 2 treatment arms (PRV-3279 versus placebo) added to limited background medications for SLE.

Number of Patients: Approximately 100 patients will be randomized to receive study drug treatment. The study will be conducted at approximately 40 sites in countries planned to include, but not limited to, United States (US), Hong Kong and China. Approximately 50 patients will be assigned to each treatment group (PRV-3279 or placebo). Randomized patients who discontinue study drug or withdraw consent for study participation will not be replaced.

Treatment Groups and Duration:

Treatment Groups:

- PRV-3279: 10 mg/kg IV infusion, administered over 2 hours, once every 4 weeks, from Week 0 to Week 20
- Placebo: 0.9% sodium chloride IV infusion, administered over 2 hours, once every 4 weeks, from Week 0 to Week 20

Duration of study participation for each patient: up to 34 weeks

- Screening: up to 6 weeks
    - ***Note:*** *The Screening period may be increased by 2 weeks, under exceptional circumstances such as delayed laboratory results or the impact of COVID-19, and upon approval by the Medical Monitor.*
- Study Treatment Period: 20 weeks
- Follow-up: 8 weeks

Central Adjudication Committee (CAC): Study integrity will be supported with remote oversight by a CAC working in tandem with study clinical and data monitors to confirm entry qualification and accuracy of disease activity scoring and to adjudicate flares.

The CAC will consist of independent medical reviewers with clinical expertise in SLE. The CAC responsibilities will include:

- Confirming patients' eligibility at Screening to enter the study
- Adjudicating SLE flare
- Ensuring the accuracy and consistency of scoring of the disease activity instruments

The CAC will be blinded to study treatment. Details of the CAC composition, objectives, and conduct will be described in the CAC charter.

Independent Data Monitoring Committee (IDMC): An IDMC consisting of 2 physicians and 1 statistician will be formed. Additionally, 1 or 2 external nonvoting advisors with experience in infectious disease, hematology, and other relevant subspecialties may be added as needed.

Throughout the study, the IDMC will continually review unblinded safety data. Meetings will be held approximately quarterly. Details of the IDMC composition, objectives, and conduct will be described in the IDMC charter.

Statistical Methods: Details of the statistical methods will be provided in the Statistical Analysis Plan (SAP).

Primary efficacy analysis:

The proportions of patients who meet the criteria of maintained improvement through Week 24 will be compared between the PRV-3279 and placebo groups using the Cochran-Mantel-Haenszel (CMH) test, accounting for randomization stratification factors. The Full Analysis Set (FAS) of randomized patients will be used.

Secondary efficacy analysis:

1. The time to treatment failure will be summarized by treatment group using Kaplan-Meier analysis (median, 95% CI, number of events, number censored, etc.) and Kaplan-Meier plots. The stratified log-rank test will be used to test for difference between treatment groups.
2. The proportion of patients who achieve the EULAR-recommended goal of low disease at Week 24 will be compared between the groups using the same test as the primary efficacy analysis.
3. The change from Screening to Week 24 in the SF-36 PCS will be analyzed using the Mixed Model for Repeated Measurements (MMRM). The model will include treatment, visit, randomization stratification factors, baseline score as fixed effects, and the treatment by visit as interaction term.
4. The proportion of patients who achieve SRI-4 at Week 24 will be compared between the groups using the same test as the primary efficacy analysis.
5. The proportions of patients who meet the BICLA criteria at Week 24 will be compared between the groups using the same test as the primary efficacy analysis.

The time to treatment failure in subgroups by stratification will be summarized by treatment using the Kaplan-Meier method and compared between treatment groups using the log-rank test.

Exploratory analysis:

Details of the exploratory analysis will be provided in the SAP.

Safety analysis:

TEAEs, SAEs, TEAEs leading to withdrawal of study drug, adverse events of special interest (AESIs), and other safety variables will be analyzed using descriptive statistics.

Immunogenicity:

ADAs will be analyzed using descriptive statistics.

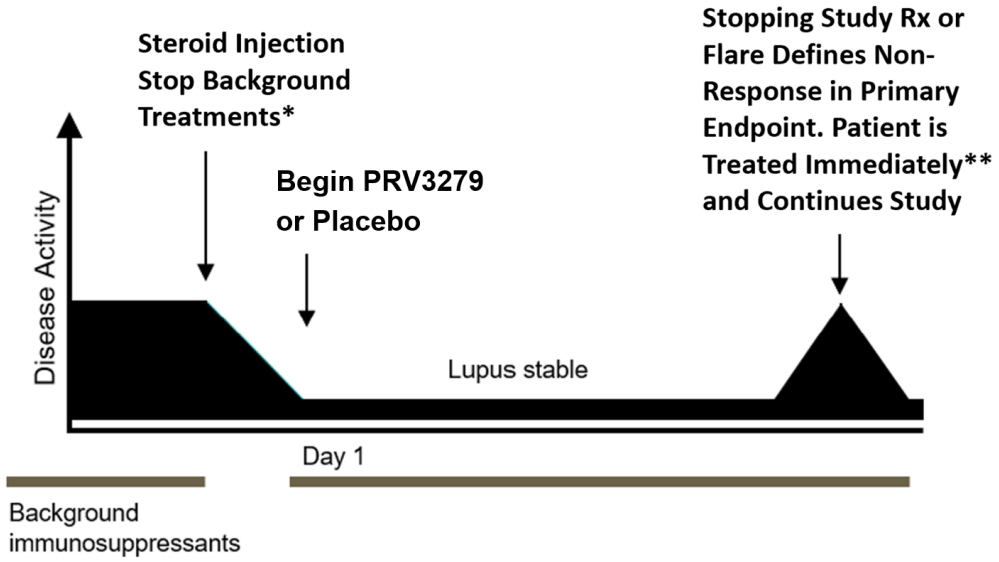
PK, PD, and PK/PD analyses:

PK and PD data will be summarized. Other exploratory analyses, [redacted], will

be detailed in the SAP. Data from this study may be combined with other PK data for a more formal population PK analysis in a separate report.

Sample Size Determination: The published data from the Phase 2, double-blind, randomized, placebo-controlled study of a reversible B cell inhibitor, XmAb®5871, in SLE showed that the response rates of the maintenance improvement in SLE signs and symptoms in the intent-to-treat (ITT) population were 40.4% vs 23.1% at Day 225 and 57.7% vs 34.6% at Day 169 for the active arm and control arm, respectively. [redacted]

1.2. Schematic



*All background SLE treatments are stopped or tapered after the Screening visit (before administration of study drug on Day 1), except prednisone up to 10 mg daily (or equivalent corticosteroid), up to 400 mg per day hydroxychloroquine [or other antimalarial]), and/or NSAIDs.

**At the time of a flare, the patient should be seen at the study site, regardless of scheduled visits.

1.3. Schedule of Activities (SoA)

Period	Screening	Randomized Treatment Visits						Follow-up		Flare Assessment Visit[1]	ET Visit
Week	-6 to -1	0	4	8	12	16	20	24	28 (EOS)		
Day	≤-42 to -1	1	29	57	86	113	141	169	197		
Visit Window (± days)			±3	±3	±3	±3	±3	±3	±3		+3
Informed consent	X										
Eligibility review	X	X									
Concomitant medications[2]	X	X	X	X	X	X	X	X	X	X	X
Complete medical history review	X										
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Vital signs[3]	X	X	X	X	X	X	X	X	X	X	X
Body weight	X	X	X	X	X	X	X	X	X	X	X
Height	X										
Complete physical exam[4]	X										
Brief physical exam[5]		X	X	X	X	X	X	X	X	X	X
Serum pregnancy test in WOCBP	X										
Urine or serum pregnancy test in WOCBP		X	X	X	X	X	X				
FSH & LH (Females – to confirm nonsurgical menopause)	X										
Hematology, chemistry, coagulation, urinalysis[6]	X	X	X	X	X	X	X	X	X	X	X
TBNK panel	X	X	X	X	X	X	X	X	X	X	X
HBV, HCV, HIV &TB tests[7]	X										
Rapid COVID-19 test	X	X	X	X	X	X	X	X	X	X	X
SLE serology tests[8]	X				X			X	X		X
SLE disease activity markers[9]	X	X	X	X	X	X	X	X	X	X	X
PK samples[10]		X	X	X	X	X	X	X	X	X	X
ADA samples[11]		X	X	X	X	X	X	X	X	X	X
[redacted]		[redacted]								[redacted]	[redacted]
PD samples[11,13]	X	X	X	X	X	X	X	X	X	X	X
Receptor Occupancy[12]		X	X	X	X	X	X	X	X	X	X

Internal

Period	Screening	Randomized Treatment Visits						Follow-up		Flare Assessment Visit[1]	ET Visit
Week	-6 to -1	0	4	8	12	16	20	24	28 (EOS)		
Day	≤-42 to -1	1	29	57	86	113	141	169	197		
Visit Window (± days)			±3	±3	±3	±3	±3	±3	±3		+3
12-lead ECG (local)	X	X	X	X	X	X	X	X	X		X
hSLEDAI, ssPGA, SFI, mSFI, BILAG, CLASI	X	X	X	X	X	X	X	X	X	X	X
CGIC		X	X	X	X	X	X	X	X	X	X
28 tender and swollen joint counts	X	X	X	X	X	X	X	X	X	X	X
SF-36, FACIT-Fatigue, PGIC/PGIS	X	X	X	X	X	X	X	X	X	X	X
Administer methylprednisolone acetate (Depo-Medrol® or equivalent) [14]	X										
Study drug administration[15]		X	X	X	X	X	X				

Abbreviations: ADA=anti-drug antibodies; ANA=antinuclear antibody; anti-dsDNA=anti-double-stranded deoxyribonucleic acid; BILAG=British Isles Lupus Assessment Group; CGIC=Clinician's Global Impression of Change; CLASI= Cutaneous Lupus Erythematous Disease Area and Severity Index; COVID=Corona virus disease 2019; ECG=electrocardiogram; ENA=extractable nuclear antigen antibody; EOS=end of study; ET=early termination; FACIT=Functional Assessment of Chronic Illness Therapy; FSH=follicle stimulating hormone; GPI=glycoprotein I, HBcAb=hepatitis B core antibody, HbsAb=hepatitis B surface antibody, HbsAg=hepatitis B surface antigen, HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; LH=luteinizing hormone; mRNA=messenger ribonucleic acid; mSFI=modified SFI; PD=pharmacodynamics; PGIC=Patient Global Impression of Change in Clinical Status; PGIS=Patient Global Impression of Change in Disease Severity; PK=pharmacokinetics; RNA=ribonucleic acid; SFI=SELENA-SLEDAI Flare Index; SF-36=Short Form 36; SLE=systemic lupus erythematosus; hSLEDAI=hybrid Systemic Lupus Erythematosus Disease Activity Index; ssPGA=SELENA-SLEDAI Physician's Global Assessment; Sm=Smith; RNP=ribonucleoproteins; SSA=Sjögren Syndrome A; SSB=Sjögren Syndrome B; TB=tuberculosis; TBNK=T cell, B cell, natural killer (NK) cell; WOCBP=women of child-bearing potential.

Footnotes:

1. Flare Assessment visits are conducted when patients experience symptoms that require assessments for a potential flare.
2. Study personnel will record all concomitant medications taken by patients, including prescription and nonprescription medications and any dietary supplements (including vitamins and minerals), nutraceuticals, herbal medicines, traditional Chinese medicines, ayurvedic remedies, and any other products.
3. Vital signs include temperature, heart rate, respiratory rate, and blood pressure. On dosing days, vital signs should be performed after patient is supine for at least 5 minutes during the 30 minutes before the study drug infusion and approximately 30 minutes after the end of infusion.
4. A complete physical exam includes (at a minimum) assessments of the head, eyes, ears, nose, throat, skin, cardiovascular, mucocutaneous, respiratory, musculoskeletal, lymphatic, gastrointestinal, and neurological systems.
5. A brief physical examination must be complete enough to be suitable for SLE instrument scoring. At a minimum, assessments will include mucocutaneous, respiratory, cardiovascular, gastrointestinal, and musculoskeletal.
6. Refer to Section 10.2 for a list of all clinical hematology, serology, coagulation, and urinalysis parameters.
7. Including HbsAg, HbsAb, HbcAb (total IgM and IgG; if positive, need HBV DNA performed), HCV RNA, HIV 1&2 (and HIV confirmation, if applicable), and QuantiFERON TB test (QuantiFERON may be repeated locally if indeterminant).

Internal

8. SLE serology tests include ANA, ENA (including antibodies against SSA, SSB, Sm, RNP), anti-cardiolipin antibodies (IgA, IgG, and IgM), anti-beta 2 GPI antibodies (IgA, IgG, and IgM), and the lupus anticoagulant.
9. SLE Disease Activity Markers: serum anti-dsDNA antibodies, complement components C3 and C4, and total serum immunoglobulin profile.
10. [redacted]
11. [redacted].
12. [redacted]
13. PD samples will include peripheral blood mononuclear cells for immunophenotype (flow), mRNA analysis including CD32B polymorphisms, and exploratory serum markers.
14. At the end of the Screening visit, if no exclusion criteria are known, a patient will receive one or more intramuscular injections of methylprednisolone acetate (Depo-Medrol® or equivalent) at a dose of ≥40 mg (maximum total dose 320 mg, maximum 4 injections). The dose will be determined by the Investigator to achieve a clinically significant improvement in SLE signs and symptoms.
15. Study drug will be administered by intravenous infusion over 2 hours. Patients will be observed for at least 2 hours after first infusion and at least 30 minutes after other infusions.

2. Introduction

2.1. Rationale

Systemic lupus erythematosus (SLE) is a chronic, multi-organ autoimmune disease with significant impact on survival, disability, and quality of life (QOL). The disease primarily affects women of childbearing age, but all age groups may be affected. According to the Lupus Foundation of America (LFA), more than 16,000 new cases of lupus are reported annually across the United States (US) with a prevalence of at least 1.5 million in the US and 5 million worldwide.

SLE is highly variable both in clinical presentation and course of the disease (Bartels 2014). Comorbidities of the disease and side effects of treatment increase the risk of morbidity and mortality in patients with SLE (Bertsias 2008). Despite major advances in understanding the pathogenesis and clinical course of lupus and improvements in overall survival, the general prognosis for lupus patients remains poor with high direct and indirect costs of the disease.

2.2. Background on PRV-3279

PRV-3279 is a humanized, Dual Affinity Re-Targeting (DART®) protein with a molecular weight of 111.5 kDa. DART proteins are bispecific, antibody-based molecules that can bind two distinct antigens simultaneously (Veri 2010). PRV-3279 is designed to target CD32B, Fcγ receptor IIb, and CD79B, the Igbeta protein that is part of the B cell receptor (BCR) complex (Veri 2010). PRV-3279 was originally developed by MacroGenics, Inc.

CD32B is a transmembrane inhibitory Fcγ receptor expressed widely on B cells and other immune effector cells. CD79B is expressed exclusively on B cells and is an essential signal transduction component of the B cell antigen receptor complex (Verschuren 1993; Dal Porto 2004). Because of the dual affinity of PRV-3279, effects are directed specifically on CD32B on B cells, which intentionally couples the B cell activation signal transduced by CD79B to the inhibitory CD32B signal. The net effect of this combined binding is the dampening of the activation of all B cell subsets, including both naïve and memory B cells, but without broad B cell depletion as measured by fluorescence-activated cell sorting (FACS) (Veri 2010).

Details can be found in the Investigator's Brochure (IB).

2.2.1. Relevance of the PRV-3279 Mechanism of Action to SLE

SLE is characterized by the emergence and persistence of pathogenic subsets of B cells and autoantibodies against multiple autoantigens, leading to unpredictable flares of inflammation in the skin, joints, and other tissues (Bartels 2014; Cancro 2009). There have been few approved treatments developed specifically for lupus, and patients must frequently rely on older, untested, untargeted immune modulators with significant safety and tolerability issues to control their disease.

B cell activation is not only prevalent but central to the pathogenesis of SLE (Zhang 2001; Stohl 2003; Chu 2009), supporting the rationale for down-modulation of B cells as a treatment of this disease. Given the need for chronic, sometimes lifelong immunosuppression in lupus, a

particularly attractive B cell-targeting therapeutic would be one that can rapidly inhibit all subsets of activated B cells but spare resting B cells from depletion. PRV-3279 has been designed to achieve this and is supported by pre-clinical data.

2.3. Nonclinical Safety

The chimpanzee is the only relevant species for nonclinical safety evaluation of PRV-3279. It is suitable for this purpose given the 100% homology of the extracellular domains of both chimpanzee and human CD32B and CD79B and the ability of PRV-3279 to both bind to and functionally inhibit human and chimpanzee B cells in a comparable manner. PRV-3279 does not bind to CD32B and CD79B in macaques or rodents, making these unsuitable species for nonclinical toxicological evaluations. Thus, the principal toxicology studies evaluating PRV-3279 included a non-Good Laboratory Practice (GLP) dose escalation toxicology study conducted in a single chimpanzee evaluating 5 doses of PRV-3279 ranging from 0.1 to 10 mg/kg followed by a recovery observation period and a GLP tissue cross reactivity study of PRV-3279 on normal human tissues. A supportive non-GLP, tissue cross reactivity study comparing the binding profile of PRV-3279 in select normal tissues from both humans and chimpanzees was also performed.

In the non-GLP toxicology study in the chimpanzee, the highest PRV-3279 dose tested (10 mg/kg) was not associated with any adverse effects, while dose-dependent pharmacodynamic (PD) outcomes were achieved. The non-GLP toxicology study in the chimpanzee was considered adequate to support initiation of a first in human, single dose study in healthy subjects (Study CP-MGD010-01).

As safety studies with PRV-3279 in other non-human primates or lower species are not feasible, MacroGenics conducted 2 GLP toxicology studies using a PRV-3279 surrogate bispecific molecule in transgenic mice lasting 4 and 13 weeks, respectively. The GLP toxicology studies were completed following the initiation of the CP-MGD010-01 study. The PRV-3279 surrogate molecule used in these studies was designed to target human CD32B and mouse CD79B in a mouse deficient (knock-out) for mouse CD32B and transgenic for human CD32B (hCD32B-Tg). In the 4-week GLP study, hCD32B transgenic mice received vehicle or the PRV-3279 surrogate molecule at a dose level of 25, 50, or 100 mg/kg/day by intraperitoneal injection daily for 27 consecutive days. Dose levels were selected to determine levels that support a safety factor above the potential target clinical dose (up to 10 mg/kg at weekly or longer intervals).

While analysis of the terminal necropsy completed on 80 mice (20 in each group) revealed no gross pathological findings, routine histopathological evaluation revealed that 2 out of 20 animals that received the surrogate molecule at 100 mg/kg/day had a right atrial thrombus. One of these animals also had a pulmonary thrombus. Evaluation of 48 animals from the recovery period (12 at each of the 4 dose levels tested) resulted in a microscopic finding of a heart thrombus in a single male that received 100 mg/kg/day. Histologically, this thrombus differed in that it appeared more fibrous with recanalization, indicating greater chronicity than those observed at the terminal necropsy. However, when considering all 3 thrombi, it is believed that they all originated during the dosing phase of the study based on histopathologic data. The incidence of thrombi in the high-dose animals of this study was approximately 9% (3 out of 32 animals) and therefore it could not be ruled out that the thrombi were a PRV-3279 surrogate related event. No other PRV-3279 surrogate-related events were identified.

Subsequently, further characterization of the transgenic mice and PRV-3279 surrogate revealed that transgenic mice have higher expression of hCD32B, specifically in peripheral blood leukocytes and cardiac endothelial tissue compared with humans, and the PRV-3279 surrogate molecule has an increased presence of dimers with increased binding to leukocyte and cardiac tissue at higher concentrations than that observed with PRV-3279. These observations associated with PRV-3279 surrogate dimers are plausible factors contributing to the observed thromboembolic events in some mice treated daily with the PRV-3279 surrogate molecule at the higher dose level of 100 mg/kg. Furthermore, it was concluded that these risks were exaggerated in or may be unique to hCD32B-Tg mice and the dosing conditions of the GLP toxicity study and likely not applicable for subjects administered PRV-3279, as supported by the lack of binding of PRV-3279 to human monocytes and cardiac endothelium.

In the 13-week GLP toxicology study, hCD32B transgenic mice received vehicle or the PRV-3279 surrogate molecule at a dose level of 10 or 50 mg/kg/day for 91 consecutive days. Dose levels were selected based on the results of the 4-week GLP toxicology study.

No effects on body weight, food consumption, or ophthalmology were observed. Although no clinical signs of toxicity were noted, treatment-related findings during functional observational battery evaluations included decreases in rearing activity, piloerection, and a decrease in body temperature in males at 50 mg/kg/day at 1-hour post-dose on Day 1 only. There were no treatment-related effects on organ weights, macroscopic observations, or microscopic observations. Mild, dose-responsive, non-adverse decreases in total protein were attributable to mild decreases in albumin and/or globulin in both sexes at ≥10 mg/kg/day, although only the decrease in globulin persisted in females at 50 mg/kg/day following recovery. The PRV-3279 surrogate molecule was well tolerated clinically when administered intraperitoneally to male and female hCD32B-Tg mice once daily for 13 weeks at doses of 10 and 50 mg/kg/day. Therefore, 50 mg/kg/day was considered the no-observed-adverse-effect level.

2.4. Phase 1 Studies of PRV-3279 in Healthy Humans

2.4.1. Single Ascending Dose Study: CP-MGD010-01

Study CP-MGD010-01 was a Phase 1, double-blind, placebo-controlled, single ascending dose (SAD) study in healthy subjects to evaluate the safety, tolerability, pharmacokinetics (PK), PD, and immunogenicity of PRV-3279. This study was divided into two parts, dose escalation and dose expansion. Dose escalation was conducted in 6 cohorts of 8 subjects each with doses of PRV-3279 increasing from 0.01 mg/kg to 10 mg/kg.

Following dose escalation, a dose-expansion phase was performed, in which doses of 3 mg/kg and 10 mg/kg of PRV-3279 were given prior to administration of the hepatitis A virus (HAV) vaccine to assess dose dependency of PRV-3279 immune modulation in the context of HAV vaccination.

2.4.1.1. Safety Results

No dose-limiting toxicities occurred in Study CP-MGD010-01. There were no adverse events (AEs) leading to study discontinuation in the dose escalation or dose expansion cohorts and no deaths occurred. No thrombotic events occurred and there were no significant laboratory abnormalities.

In summary, single-dose intravenous (IV) infusions of 0.01 to 10 mg/kg PRV-3279 were well tolerated. Review of the clinical laboratory data did not reveal any direct laboratory toxicity related to PRV-3279 administration. Laboratory abnormalities were not clinically significant, dose dependent, or reported as AEs.

2.4.1.2. Pharmacokinetic Results

In the dose escalation phase of CP-MGD010-01, PRV-3279 exhibited nonlinear PK over the single IV dose range of 0.01 to 10 mg/kg in healthy subjects. Exposure, in terms of area under the concentration-time curve (AUC), increased in a more than dose-proportional manner with increasing dose. Clearance (CL) and volume of distribution decreased with increasing dose. There was low variability in exposure parameters (%CV < 27%). The mean CL, volume of distribution (Vd), and half-life ($t_{½}$) of PRV-3279 were approximately 0.35 mL/h/kg, 68 mL/kg, and 191 h (~8 days), respectively, for the 10 mg/kg single dose. In the dose escalation phase, maximum serum concentration (C_{max}) of PRV-3279 and overall exposure (AUC) increased in a dose-related manner, with median time to C_{max} (T_{max}) ranging from 1.98 to 6.00 h between 0.01 and 10 mg/kg.

2.4.1.3. Immunogenicity Results

Single doses of PRV-3279 were immunogenic in healthy subjects. The first appearance of anti-drug antibodies (ADAs) occurred on Day 15 or later. No placebo-treated subject had ADA-positive samples either pre-dose or post-dose. There was an apparent decrease in ADA incidence and titers with increasing dose of PRV-3279. The presence of ADA to PRV-3279 had no detrimental effect on single-dose PK, as assessed by comparing the PK parameters of ADA-positive and negative subjects. Immunogenicity of PRV-3279 had no detrimental effect on single-dose PK.

2.4.1.4. Pharmacodynamic Results

PRV-3279 displayed dose-dependent target B cell binding in the periphery. Following infusion of ≥0.1 mg/kg, PRV-3279 binding to B cells was at least 50% of its maximal level with durations ranging from 7 to 56 days, again depending on dose. Previous *in vitro* studies have demonstrated that PRV-3279-mediated inhibitory function of B cells reaches optimal effect when >50% of maximal PRV-3279 binding to human B cells is achieved.

Peripheral B cells collected from subjects following a single administration of PRV-3279 at ≥1 mg/kg displayed inhibited *ex vivo* response to B cell activation as measured by the calcium flux response, with the extent and duration of inhibition correlating with PRV-3279 dose. PRV-3279 was not associated with B cell depletion as measured by FACS but B cells exhibited dose-dependent down-modulation of surface BCR and the co-stimulation molecule CD40.

In the dose expansion phase, the effect of PRV-3279 on humoral responses to HAV vaccination was investigated. Seroconversion rates and mean serum titers of HAV-IgG were reduced at both the 3 mg/kg and 10 mg/kg doses, as compared to placebo. Delayed HAV-IgG seroconversion was also observed in the 10 mg/kg PRV-3279 dose group.

PRV-3279 did not result in B cell activation, B cell depletion, or systemic cytokine release, at any dose. Taken together, these results demonstrate that administration of PRV-3279 inhibits B cell activation and function, consistent with its designed mechanism of activation.

2.4.2. Multiple Ascending Dose Study (PREVAIL-1)

The multiple ascending dose (MAD) study (PREVAIL-1) was designed to assess the safety and tolerability of PRV-3279 given as three infusions at two dose levels (3 and 10 mg/kg). Secondary objectives were to characterize the multidose PK and the immunogenicity of PRV-3279. Exploratory objectives included exploration of the effects of PRV-3279 on potential biomarkers for target engagement and B cell function.

Sixteen healthy subjects were enrolled. Each cohort of 8 subjects received PRV-3279 or placebo at a ratio of 3:1 (n=6 for PRV-3279 and n=2 for placebo). Fourteen subjects received all planned treatments per protocol and completed the study.

2.4.2.1. Safety Results

PRV-3279 was well tolerated. There were no AEs of special interest (AESIs), serious adverse events (SAEs), or treatment-emergent adverse events (TEAEs) leading to death. One (16.7%) subject who received PRV-3279 10 mg/kg had 4 mild TEAEs considered by the Investigator to be related to the study drug (abdominal pain, feeling hot, cold sweat, and hyperhidrosis), and the subject withdrew from the study due to these TEAEs. A total of 34 TEAEs were reported in 9 (56.3%) subjects. The most frequently reported TEAEs excluding catheter or venipuncture site AEs were feeling hot (3 TEAEs) and cold sweat (2 TEAEs each). All other TEAEs were reported once each. Two TEAEs were moderate in severity, and the remainder were mild. All out-of-range clinical laboratory values, vital signs measurements, electrocardiogram (ECG) results, and physical examination findings were evaluated as not related to the study drug and not clinically significant; none were reported as TEAEs.

2.4.2.2. Pharmacokinetic Results

The $t_{1/2}$ on Day 29 was 157 h (6.54 days) and 185 h (7.71 days) for the 3 mg/kg and 10 mg/kg dose levels, respectively. The volume of distribution at steady state (V_{ss}) was comparable for the 3 mg/kg and 10 mg/kg doses (618 mL/kg and 576 mL/kg). CL on Day 29 was slightly lower for the 10 mg/kg dose (1.63 mL/h/kg) than for the 3 mg/kg dose (2.71 mL/h/kg).

After multiple dosing to Day 29, there was minimum accumulation of PRV-3279 as shown by accumulation ratios based on C_{max} ($RacC_{max}$) and AUC ($RacAUC_{0-336}$) values for the 3 and 10 mg/kg doses of 1.08 and 1.25 and 1.33 and 1.49 levels, respectively. The geometric mean (GM) V_{ss} on Day 29 was comparable for the 3 mg/kg and 10 mg/kg dose levels (61.8 mL/kg and 57.6 mL/kg). The GM CL on Day 29 was lower for the 10 mg/kg dose (0.163 mL/h/kg) compared to the 3 mg/kg dose (0.271 mL/h/kg). The V_{ss} and CL on Day 29 in this study compare favorably to the corresponding values observed in the dose escalation phase of the SAD study (63.0 and 67.6 mL/kg and 0.39 and 0.35 mL/h/kg, for the 3 and 10 mg/kg dose levels, respectively).

2.4.2.3. Immunogenicity Results

Consistent with the mechanism of action and ability of PRV-3279 to inhibit its own immunogenicity, incidence of ADA was higher at 3 mg/kg (6 out of 6) compared to 10 mg/kg (4 out of 6) at the end of the study. The assay used was validated and drug tolerant (not affected by the presence of PRV-3279). The ADA titers were generally low. Although the numbers of subjects per cohort provide a small sample size, there was no apparent effect of ADA on PK variables. Evaluation of the mean serum concentrations of PRV-3279 by ADA results shows a trend for slightly higher concentrations up to about Day 43 at the 3 mg/kg dose when ADA are positive. No trend can be identified for the 10 mg/kg dose due to limited data. The number of ADA-positive subjects increased over time. At the 3 mg/kg dose level, the first subject with a positive result was on Day 15. All 6 subjects of this dose level tested positive on Day 85. At the 10 mg/kg dose level, the first subject who tested ADA positive was on Day 36. On Day 85, 4 of the 6 subjects were ADA positive.

2.4.2.4. Pharmacodynamic Results

After initial dosing with 3 and 10 mg/kg PRV-3279, >85% total number of available CD19+ peripheral blood B cells were bound. The binding pattern was similar for memory B cells (CD19+/CD27+) and naïve B cells (CD19+/CD27-). Binding intensity to B cells by PRV-3279 did not differ in different B cell subpopulations and was slightly higher for 10 mg/kg than 3 mg/kg, At the 10 mg/kg dose, levels of >50% receptor occupancy, which is considered the minimum level of binding required for optimal B cell modulation, were detected for up to 28 days after the final dose. Both groups declined to approximately baseline levels at Day 85. Due to sample instability, these percent binding values were likely underestimated.

PRV-3279 treatment was associated with a decrease in IgM production by -35% to -44%, which persisted until the end of the study. There was a dose-response trend, with the 10 mg/kg achieving greater reductions in IgM and also showing a reduction in IgE. No drug effect was observed on IgG levels. This was expected given that there was no concurrent antigen stimulus and IgG $t_{½}$ is longer than the other classes. Peripheral B cell counts showed short-term (<24 hours) reduction of <50%, and no abnormalities were seen in other immune cell types. No cytokine release was measurable after dosing with PRV-3279.

Taken together with the PK/PD effects and safety observed in CP-MGD010-01, these results are consistent with the hypothesis that repeat administration of PRV-3279 can safely and durably inhibit B cell function and humoral immune responses without depletion of B cells in the peripheral blood, and support further evaluation of PRV-3279 for modulating autoantibody production by B cells in an autoimmune disease setting such as SLE.

Circulating immunoglobulin levels were also measured. IgM levels steadily decreased throughout the dosing period in both the 3 and 10 mg/kg dose groups and remained decreased at the last measurement on Day 85. Decreases were dose dependent, with the greatest mean percentage change from baseline being -34.5% for 3 mg/kg and -43.9% for 10 mg/kg at Day 85, compared to -1.3% in placebo-treated subjects. IgG levels were not affected by dosing with PRV-3279.

In summary, repeat dosing of PRV-3279 demonstrated a profound and durable modulation of B cells in this study, affecting humoral immunity without B cell depletion or cytokine stimulation, supporting and further extending the PD observations made in the SAD study.

2.5. Risk-Benefit Assessment

The PREVAIL (PRV-3279 EVAluation In Lupus) program is designed to evaluate PRV-3279 for treatment of patients with SLE. Non-human GLP toxicology studies support the predicted mechanism and its potential as a treatment for SLE. Specifically, per feedback from the US Food and Drug Administration (FDA), 4- and 13-week intraperitoneal toxicology studies with a PRV-3279 surrogate molecule provide adequate characterization (hazard identification) with respect to potential toxicities of PRV-3279 in human subjects and offer sufficient nonclinical support for longer clinical trials.

An initial SAD study of PRV-3279 in healthy subjects (CP-MGD010-01) demonstrated good safety and tolerability of PRV-3279 given IV from 0.1 to 10 mg/kg, along with favorable PK and PD characteristics. Proof of mechanism (B cell inhibition) was demonstrated in a dose-expansion cohort, in which doses of 3 and 10 mg/kg were given before HAV vaccine. PRV-3279 reduced HAV seroconversion and specific antibody titers. In this study, high levels of immunogenicity to PRV-3279 were observed as measured by ADA levels. The ADA levels were inversely proportional to dose, suggesting PRV-3279 may inhibit its own immunogenicity.

In the PREVAIL-1 MAD study, the safety, tolerability, and immunogenicity of PRV-3279 were evaluated in healthy subjects at dose levels projected to provide sustained high-level receptor coverage. Healthy subjects were chosen to avoid confounding effects of background disease and concomitant medications. At both 3 and 10 mg/kg, PRV-3279 was well tolerated and bound >85% total B cells, including both memory B cells and naïve B cells. At the 10 mg/kg dose, levels of >50% receptor occupancy consistent with optimal B cell modulation, were detected for up to 28 days after the final dose. Expected reductions of IgM but not IgG levels were observed. Immunogenicity (ADA) was again observed to be less common at the higher dose. PRV-3279 was well tolerated. There were no SAEs, and only one subject had TEAEs leading to withdrawal of study drug (abdominal pain, feeling hot, cold sweat, and hyperhidrosis).

The current PREVAIL-2 study is designed to ensure that SLE patients with active symptoms can be assessed for both safety and potential efficacy with PRV-3279. Significant disease activity is required at Screening, but subjects with organ-threatening disease will be excluded so that background medications can be significantly restricted to better evaluate safety, PK/PD, and efficacy of PRV-3279. The restriction on background SLE medications can also minimize placebo-response rates, increasing the power and interpretability with a smaller trial and minimizing potential drug-drug interactions or additive immunosuppressive effects. This smaller trial design reduces the number of subjects exposed to PRV-3279 in early development when any potential benefit is uncertain.

In this study, PRV-3279 will be administered at a dose of 10 mg/kg once every 4 weeks in SLE patients, which is based upon supportive PK and PD data from PREVAIL-1. Initial observations found 10 mg/kg to be well tolerated and less immunogenic than lower doses of PRV-3279. The safety data from the short-term SAD and MAD PK studies in healthy volunteers is reassuring but long-term effects of prolonged dosing on immunoglobulins and other immune factors are

currently unknown. A risk mitigation strategy that has been successful in other trials of B cell modulators will be put into place, which includes ensuring locally appropriate vaccinations are up to date prior to study entry, detailed safety monitoring, as well as early recognition and treatment for infections.

A key aspect of this Phase 2a study will be to study the immunologic mechanisms of PRV-3279 in SLE and to develop an understanding of potential patient subsets for whom the drug might be more or less effective. As well as monitoring for the effect of CD32B polymorphisms, PD data recently released to the public domain on obexelimab (XmAb®5871), a different biologic agonist of FcγRIIb (Merrill 2020), provide a unique opportunity to test a pre-specified, evidence-based PD hypothesis in this early phase trial. Specifically, we will assess whether the greatest treatment effect will be found in a subset of patients with a phenotype characterized by low expression of gene signatures associated with inflammation, coupled to elevated expression of B cell signature pathways. The study population will not be restricted to these patients, but for patients in geographic regions with access to a rapid gene expression profiling system at Screening, the presence or absence of elevated expression of B cell signature pathways will be one of the stratification factors during randomization.

The risk-benefit assessment can be summarized as follows:

1. Favorable safety profile with short-term use in healthy subjects
2. Risk mitigation strategy to address unexpected risks of longer treatment
3. Existing evidence that the treatment achieves its targeted mechanism
4. Sound rationale to test this mechanism in SLE
5. A trial design that minimizes background medications in order to:
    a. Restrict study entry to patients with non-organ-threatening disease and provide immediate flare assessment and treatment by a Central Adjudication Committee (CAC)
    b. Support an interpretable small trial, which exposes fewer patients to an early phase investigational drug
    c. Achieve clarity in PD assessments
    d. Reduce the risk for infections and toxicities due to drug combinations
6. An independent Data Monitoring Committee (IDMC) to monitor safety throughout the study.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	

To evaluate the ability of PRV-3279 to prevent flare, i.e., to maintain the improvement in SLE signs and symptoms for 24 weeks, after the amelioration of active disease induced by corticosteroid treatment before Day 1 with the withdrawal of major background medications.	Proportion of patients who maintain the improvement in SLE disease activity from Baseline (Day 1) to Week 24, defined as no lupus flare during this period.
	A lupus flare is defined as:
	• Investigator's assessment that the SLE activity meets the LFA international consensus definition for a flare[1] **AND**
	• A score of "definite worsening" or "severe worsening" on Clinician's Global Impression of Change (CGIC), **AND**
	• at least one of the following occurrences
	  ○ an increase of ≥4 points from baseline in the hybrid Safety of Estrogens in Lupus Erythematosus National Assessment -Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score (hSLEDAI), **OR**
	  ○ ≥1 organ with an A score (severe) or B Score (moderate) item rated new or worse on British Isles Lupus Assessment Group (BILAG) Index

Secondary	
Efficacy: 1. To evaluate whether PRV-3279 prolongs the duration of disease amelioration induced by corticosteroids before Day 1.	1. Time to treatment failure. Treatment failure is defined compared to Baseline (Day 1): • Occurrence of an SLE flare (as defined in the primary endpoint), **OR** • Missing 2 consecutive doses or 3 or more total doses of the study drug for any reason, **OR**

Objectives	Endpoints
	• Initiation of a new SLE medication, **OR** • Increased dose of current SLE medication, with the exception of nonsteroidal anti-inflammatory drugs (NSAIDs), **OR** • Patient withdrawal from the study before the Week 24 visit
2. To determine whether PRV-3279 allows patients to achieve and sustain European League Against Rheumatism (EULAR)-recommended treatment goal of low disease.	2. Proportion of patients who meet either of the following criteria at Week 24: • Hybrid SELENA-SLEDAI (hSLEDAI) score <3 **OR** • All BILAG scores are C or less
3. To evaluate the effect of PRV-3279 on patient-reported physical functioning.	3. Change from Screening to Week 24 in the Physical Component Score (PCS) in the Short Form 36 Health Survey (SF-36).
4. To determine whether PRV-3279 can reduce one or more signs and symptoms of SLE using a stringent definition for improvement in each sign or symptom, based on the SLE Responder Index-4 (SRI-4)	4. Proportion of patients who meet the criteria for SRI-4 at Week 24 compared to Screening. SRI-4 is defined as: • A hSLEDAI score decrease of ≥4 points, **AND** • No new organs with a BILAG A (severe) score, **AND** • No more than 1 new organ with a BILAG B (moderate) score, **AND** • No SELENA-SLEDAI Physician's Global Assessment (ssPGA) score increase of >0.3 points.
5. To determine whether PRV-3279 reduces disease activity in all organs that are rated as moderately or severely active at Screening using the BILAG Index.	5. Proportion of patients who meet the BILAG-based Combined Lupus Assessment (BICLA) criteria at Week 24 compared to Screening: • Reduction by ≥1 grade in all organs with BILAG A or B scores **AND** • No worsening of SLEDAI or other BILAG organs **AND**

Objectives	Endpoints
	• No ssPGA score increase of ≥0.3 points.
Safety: To evaluate the safety and tolerability of PRV-3279.	Frequency of TEAEs, SAEs, TEAEs leading to drug withdrawal, AESIs, and total serum immunoglobulin levels. Frequency of potentially clinically important changes in clinical laboratory tests, vital signs, ECGs, and physical examinations.
PK and Immunogenicity: To evaluate the PK and immunogenicity of PRV-3279 in patients with SLE.	Serum concentrations of PRV-3279. ADA titers.
Exploratory	
[redacted]	[redacted]

1. "A flare is a measurable increase in disease activity in one or more organ systems involving new or worse clinical signs and symptoms and/or laboratory measurements. It must be considered clinically significant by the assessor, and usually, there would be at least consideration of a change or an increase in treatment." (Ruperto 2011)

4. Study Design

4.0. Design

This is a randomized, double-blind, placebo-controlled study in adult patients with active SLE. Approximately 100 eligible patients will be randomized at a 1:1 ratio to receive treatment with either 10 mg/kg PRV-3279 or placebo. The study drug, PRV-3279 or placebo, will be given as an IV infusion over 2 hours, every 4 weeks from Week 0 through Week 20, inclusive, for a total of 6 doses. Two follow-up visits are planned (Week 24 and Week 28). The end of study (EOS) visit will occur at Week 28.

Study integrity will be supported with remote oversight by a CAC working in tandem with study clinical and data monitors to confirm entry qualification and accuracy of disease activity scoring and to adjudicate flares (see Section 8.2.6.1). The CAC members will be blinded to study treatment assignment. Details are provided in the CAC charter.

During the Screening period, the patient will receive an intramuscular (IM) injection of methylprednisolone acetate (Depo-Medrol® or equivalent) at a dose of ≥40 mg to induce improvement of SLE signs and symptoms. Repeat injections may be given to further ameliorate symptoms, up to a total of 4 injections with a maximum total dose of 320 mg.

Starting on Day 1 (Baseline/Randomization visit) and continuing throughout the study the only background SLE treatments that may be continued are hydroxychloroquine up to 400 mg per day (or other antimalarial [Section 10.5]), up to 10 mg per day prednisone (or equivalent corticosteroid [Section 10.5]), and NSAIDs. Patients will be asked to abstain from NSAIDs on the mornings of the Randomization visit and all subsequent visits (NSAIDs can be re-started after completing all evaluations on the day of each study visit). On other days throughout the study, NSAIDs are allowed without restrictions. All other SLE treatments taken at the time of Screening will be withdrawn during the Screening period and prior to Randomization.

Potentially eligible patients will return to the study site to confirm eligibility for randomization on Day 1. The Investigator must confirm that the patient has achieved at least a moderate improvement in SLE signs and symptoms as indicated by:

CGIC score of "definite improvement" or "major or complete improvement"

AND

≥4-point decrease in hSLEDAI score from Screening, **OR** improvement by ≥1 severity grade in at least one BILAG system that was severe (A score) or moderate (B score) at Screening (i.e., from A to B-D or from B to C or D).

Note: Assessments by hSLEDAI and BILAG Index at the Randomization visit may not follow the standard 4-week assessment rules but will be scored by a simple clinical comparison of SLE disease activity at Week 0 (Day 1, Randomization Visit) and the Screening Visit.

If the patient is confirmed eligible, randomization will occur through an interactive voice/web response system (IVRS/IWRS). [redacted]

At each visit, formal assessments of disease activity and safety will be conducted, and laboratory specimens will be collected. Patients will receive IV infusions of the study drug every 4 weeks from Week 0 through Week 20, inclusive.

All efforts should be made to retain all patients in the study, regardless of their compliance with study procedures. If a patient takes any new SLE medications (other than NSAIDs), increases the dose of current SLE medications (other than NSAIDs), misses 2 consecutive doses or 3 or more total doses of the study drug, the site should contact the Medical Monitor to discuss permanent discontinuation of the study drug. The patient will be encouraged to continue study procedures and assessments, but will be documented as a nonresponder in the primary and applicable secondary efficacy endpoints.

If a lupus flare occurs (as defined in the primary endpoint [Section 1.1 and Section 3]), the patient should contact the study site immediately and be seen as soon as possible for a Flare Assessment visit, regardless of visit schedule, and should be assessed according to the Schedule of Activities (SoA) (Section 1.3). SLE medications may be prescribed as warranted to control the symptoms and/or signs present at this visit (Section 6.6.3). If confirmed, the patient will discontinue any further study drug administration and will be considered a nonresponder in the primary and applicable secondary efficacy endpoints.

Throughout the study, SLE disease activity and patient -reported outcomes (PROs) will be assessed using the following instruments:

- Disease Activity Instruments:
  - The hybrid Safety of Estrogens in Lupus Erythematosus National Assessment Systemic Lupus Erythematosus Disease Activity Index (hSLEDAI)
  - The SELENA-SLEDAI Physician's Global Assessment (ssPGA)
  - SELENA-SLEDAI Flare Index (SFI)
  - Modified SELENA-SLEDAI Flare Index (mSFI)
  - British Isles Lupus Assessment Group (BILAG) Index
  - Clinician's Global Impression of Change (CGIC)
  - Cutaneous Lupus Erythematous Disease Area and Severity Index (CLASI)
  - Tender and swollen joint counts
- PROs:
  - Short Form 36 Health Survey (SF-36)
  - Patient Global Impression of Change in Clinical Status (PGIC)
  - Patient Global Impression of Change in Disease Severity (PGIS)
  - Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue Scale)

Safety assessments will include TEAEs, vital signs, physical examination findings, 12-lead ECGs, and clinical laboratory tests (hematology, chemistry, urinalysis, coagulation panel, lupus-related serologies, SLE disease activity markers, and T cell, B cell, natural killer cell [TBNK] panel). A urine or serum pregnancy test will be performed for women of childbearing potential (WOCBP) onsite prior to each study drug administration (serum pregnancy test at Screening).

PK (serum PRV-3279 concentrations), PD (biomarkers) and immunogenicity assessments will also be conducted.

Disclosure Statement: This is a Phase 2a, double-blind, placebo-controlled trial with 2 treatment arms (PRV-3279 versus placebo) added to limited background medications for SLE.

Number of Patients: Approximately 100 patients will be randomized to receive study drug treatment. The study will be conducted at approximately 40 sites in countries planned to include, but not limited to, US, Hong Kong, and China. Approximately 50 patients will be assigned to each treatment group (PRV-3279 or placebo). Randomized patients who discontinue study drug or withdraw consent for study participation will not be replaced.

Treatment Groups and Duration:

Treatment Groups:

- PRV-3279: 10 mg/kg IV infusion, administered over 2 hours, once every 4 weeks from Week 0 through Week 20, inclusive
- Placebo: 0.9% sodium chloride IV infusion, administered over 2 hours, once every 4 weeks, from Week 0 through Week 20, inclusive

Duration of study participation for each patient: up to 34 weeks

- Screening: up to 6 weeks
  - ***Note:*** *The Screening period may be increased by 2 weeks, under exceptional circumstances such as delayed laboratory results or the impact of COVID-19, and upon approval by the Medical Monitor.*
- Study Treatment Period: 20 weeks
- Follow-up: 8 weeks

4.1. Scientific Rationale for Study Design

This double-blind, placebo-controlled study will randomize approximately 100 patients with moderate to severe, but non-organ-threatening SLE disease activity. To qualify, patients must demonstrate protocol-specified disease improvement after injection of methylprednisolone acetate (Depo-Medrol® or equivalent) and withdrawal of all pre-screening SLE treatments except up to 400 mg per day for hydroxychloroquine (or other antimalarial [Section 10.5]), NSAIDs, and/or up to 10 mg prednisone (or equivalent corticosteroid [Section 10.5]). Patients will be randomized to receive 10 mg/kg PRV-3279 or placebo for 20 weeks to determine which group has a greater proportion of responders, defined as reaching Week 24 with no lupus flare activity while continuing study treatment and without receiving any SLE medications to treat a flare (as defined in Section 6.6.3).

This study was designed to utilize several innovations in previous SLE clinical trial designs (Merrill 2018a), such as the use of corticosteroid injection during Screening to provide temporary relief of symptoms in all patients before withdrawing background medications and initiating study treatment as well as a CAC committee.

4.2. Justification for Dose

[redacted]

[redacted]

4.3. Definition of End of Study

The end of the study is defined as the last patient has completed the last visit in the study.

5. Study Population

Eligibility must be confirmed by the CAC (Section 8.2.6.1), which will review each patient's Screening information provided by the Investigator. Details are provided in the CAC Charter.

5.1. Inclusion Criteria

Patients must meet all of the following criteria for study inclusion:

1. Able to understand and willing to sign the informed consent form (ICF), which is written in a language in which the patient is fluent.
2. Ages 18 to 70 years, inclusive, at Screening.
3. Have had a diagnosis of SLE for at least 6 months prior to the Screening visit.
4. Meet the 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) criteria for SLE at Screening.
5. Have moderate to severe disease activity despite stable standard-of-care medication, defined as:
   a. At Screening: hSLEDAI score ≥6 (≥4 points of which must come from non-serological finding), OR at least one BILAG A or one B score. Additionally, in the opinion of the Investigator and the CAC, the patient has adequate active reversible disease to warrant participation in a clinical trial of an investigational biologic and adequate stability to tolerate a protocol in which immunosuppressives are withdrawn.
   b. At Randomization: Patients meet the following definition for improvement:
      1) ≥4-point drop in hSLEDAI, OR one BILAG letter grade improvement in at least one A or B score present at Screening, AND
      2) Investigator rates the CGIC as "definite improvement" or "major or complete improvement."
6. Documented history of positive antinuclear antibody (ANA) and at least one of the following serologic parameters within the Screening period:
   a. Positive ANA ≥1/160
   b. ≥1 positive anti-extractable nuclear antigen antibody (ENA) test (Ro, La, Sm, RNP)
   c. Positive serum anti-dsDNA antibodies elevated to above normal (borderline results are not accepted)
   d. Complement components C3 or C4 below cutoff value attributed to lupus activity.
7. Able and willing to receive methylprednisolone acetate (Depo-Medrol® or equivalent) injection(s) ≥40 mg during the Screening period sufficient to cause clinically significant disease improvement.
8. Able and willing to stop all lupus treatments except for the following: up to 400 mg per day hydroxychloroquine (or other antimalarial [Section 10.5]) if these have been taken for at least 2 months prior to Screening at stable dose and well tolerated and/or up to 10 mg per day prednisone (or equivalent corticosteroid [Section 10.5]) if these have been taken for at least two weeks prior to Screening. Stable doses of prednisone of up to 15 mg at Screening are permitted if they can be tapered to 10 mg or less during the Screening period after given the methylprednisolone acetate (Depo-Medrol® or equivalent)

injection(s) and prior to randomization. NSAIDs may be continued or may be initiated or taken as needed at any time during the study, but must be withheld on the morning prior to Day 1 and subsequent visits.

9. A female patient is eligible to participate if she is not pregnant, is not breastfeeding, is not planning to become pregnant during the study; and at least one of the following conditions must apply:
   - Not a WOCBP (Section 10.4), or
   - A WOCBP who agrees to follow the contraceptive guidance (Section 10.4) during the entire study through at least 8 weeks after the last dose of the study drug.
10. WOCBP must have a negative serum pregnancy test at the Screening visit and must have a negative urine or serum pregnancy test at the Randomization visit prior to the first dose of study drug. Note: Patients with borderline serum pregnancy tests at Screening must have a serum pregnancy test ≥3 days later to document a negative result.
11. Sexually active men with heterosexual partners who are WOCBP must agree to adhere to the same effective birth control methods as defined in Section 10.4, and must not plan to start a family during the study.
12. Both men and women must agree to abstain from donating blood, sperm, or eggs during the study through at least 8 weeks after the last dose of study drug.
13. Patient is not incarcerated and is not compelled to participate in the study.
14. After evaluation of screening data by the CAC, the patient is deemed to have a convincing diagnosis of SLE, have adequate active disease to justify potential treatment with an investigational biologic, and is medically stable enough to participate in the protocol.

5.2. Exclusion Criteria

Patients must not meet any of the following criteria to be eligible:

1. Currently receiving induction treatment or maintenance treatment (e.g. mycophenolate mofetil, azathioprine, JAK inhibitor, calcineurin inhibitor, others)for lupus nephritis.
2. Have active lupus nephritis defined as urinary protein >1 g per 24 hours, or new onset proteinuria >500 mg per 24 hours without a diagnostic workup to rule out nephritis. NOTE: Protein/creatinine ratio may be used as an approximate surrogate for a 24-hour urine collection, and 500 mg/g or 56.6 mg/mmol is considered equivalent to 500 mg/day.
3. Have active central nervous system (CNS) manifestations of SLE, including seizure, psychosis, encephalopathy, cerebrovascular accident, or any evidence of active CNS vasculitis within 4 months of the Screening visit and up to and including the Randomization visit.
4. Have other inflammatory or autoimmune diseases that, in the opinion of the Investigator or CAC, may confound efficacy evaluations. These might include but should not be limited to psoriatic arthritis, Lyme disease, or other infectious arthritis, multiple sclerosis, or scleroderma.
5. Common variable immunodeficiency syndrome or any other clinically significant immunodeficiency (per Investigator or CAC judgment).

6. Liver function: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2.5 times the upper limit of normal (ULN).
7. Complete blood count (CBC):
    a. white blood cell (WBC) count $<1.5\times10^9$/L;
    b. lymphocyte count $<0.3\times10^9$/L (If lymphocyte count is $<0.5\times10^9$/L, a repeat sample must be collected and analyzed and must not be decreasing.);
    c. neutrophil count $<1.0\times10^9$/L;
    d. hemoglobin ≤8.0 g/dL;
    e. platelet count $<40\times10^9$/L (If the platelet count is $<70\times 10^9$/L, a repeat sample must be collected and analyzed and must not decrease $>5\times10^9$ /L within the Screening period.)
8. Renal function: serum creatinine >2 mg/mL.

Note: Abnormal laboratory tests meeting exclusion criteria may be repeated once during Screening.

9. Hepatitis B virus (HBV):
    a. Hepatitis B surface antigen (HBsAg) positive; or
    b. Total hepatitis B core antibody (HbcAb) positive (IgM and IgG) and HBV DNA positive. (HBV DNA will be used as a reflex test if total HbcAb is positive. Those with negative HBV DNA may be included in the study.)

    Note: Hepatitis B surface antibody (HbsAb) will also be performed at Screening to confirm presence of prior infection or vaccination but is not exclusionary.
10. Hepatitis C virus (HCV): Patients with positive HCV RNA.
11. Known COVID-19 infection in the 4 weeks before Screening or positive SARS-CoV-2 test (any matrix) during Screening.
12. History of allergic reaction to any human-derived biological product.
13. Received a live attenuated vaccine within 2 months of Screening, or received a non-live or mRNA vaccine within 2 weeks of Screening. Patients should be advised to delay vaccines until after the study completion to ensure optimal vaccine efficacy; however, receipt of a non-live vaccine after randomization is not exclusionary.
14. Participated in any interventional clinical trial within 42 days prior to Screening or within five half-lives of the investigational product, whichever is longer.
15. Received rituximab or equivalent treatment that depletes B cells within 6 months of Screening unless return of B cells to pre-treatment value or normal range can be demonstrated.
16. Received tumor necrosis factor inhibitors, interleukin antagonists, or other biologics, including belimumab, within 42 days or five half-lives of the agent, whichever is longer.
17. Received IV immunoglobulin (IVIG) or IV cyclophosphamide within 2 months, prednisone ≥ 100 mg/day for more than 30 days within 2 months, or plasmapheresis within two months of the Screening visit.
18. Any episode of herpes zoster virus (HZV) infection within 2 months or >2 episodes within the past 2 years unless the patient has been vaccinated for HZV.

19. Any recent infection requiring antibiotics within two weeks of Screening or any recent infection requiring IV antibiotics or hospitalization within 1 month of Screening.
20. Previous close contact with a person with active tuberculosis (TB) without receiving satisfactory anti-TB treatment as per World Health Organization (WHO) or national guidelines or history, or current diagnosis, of active TB, or untreated latent TB infection (LTBI), defined by a positive QuantiFERON TB-Gold test at the Screening visit.
    A. Indeterminate QuantiFERON TB-Gold may be repeated once (repeat testing may be performed locally). If the second test is negative, the patient will be considered negative. If the second test is also indeterminate, the patients may be allowed to participate in the study if chest x-ray confirms no active disease, and one of the following conditions is met:
        i. Active TB is ruled out by a specialist or pulmonologist who is familiar with diagnosing and treating TB (as acceptable per local practice).
        ii. The patient has documented evidence of satisfactory completion of LTBI-appropriate prophylaxis as per WHO or national guidelines within the last 5 years following review by a physician specializing in TB.
        iii. The patient has completed at least 4 weeks of LTBI-appropriate prophylaxis prior to randomization with agents recommended as preventative therapy for LTBI according to country-specific/CDC guidelines and is willing to complete the entire course of recommended LTBI therapy.
    B. QuantiFERON TB-Gold-positive patients may be allowed to participate in the study if all the following are true:
        i. Chest x-ray confirms no active disease,
        ii. The patient has completed at least 4 weeks of LTBI-appropriate prophylaxis prior to randomization with agents recommended as preventative therapy for LTBI according to country-specific/Centers for Disease Control and Prevention (CDC) guidelines and is willing to complete the entire course of recommended LTBI therapy, and
        iii. The CAC confirms the patient to be stable for inclusion.
21. Non-TB mycobacteria, opportunistic infections (e.g., cytomegalovirus, pneumocystis pneumonia, aspergillus, histoplasma, coccidioidomycosis) within 6 months prior to Screening.
22. History of or treatment for any malignancy within the past 5 years, except non-melanoma skin cancers.
23. Known human immunodeficiency virus (HIV) infection or history of clinically significant immunodeficiency.
24. History of solid organ transplant or bone marrow transplant.
25. Active substance abuse in the past year in the opinion of the Investigator.
26. Any condition for which, in the opinion of the Investigator or CAC, participation in the study would not be in the best interest of the patient (e.g., compromise their well-being) or that could prevent, limit, or confound the protocol-specified assessments.

5.3. Screen Failures

Screen failures are defined as patients who consent to participate in the study but are not subsequently randomly assigned to study treatment. Minimal information required for documentation includes demography, screen failure details, eligibility criteria, and any SAEs.

Patients with screening laboratory tests that are out of the eligibility ranges may be re-tested once during screening.

If re-screening is appropriate, the Investigator must contact the Medical Monitor to discuss the reason for screen failure and eligibility for re-screening.

6. Study Treatment

In this protocol, the investigational products, i.e., study drugs, are PRV-3279 and placebo (0.9% sodium chloride).

6.1. Study Drug Administration

The PRV-3279 drug product is a sterile, preservative-free solution for IV administration supplied at a protein concentration of 4 mg/mL in a single-dose vial containing 20 mg/5 mL (extractable content). PRV-3279 10 mg/kg will be administered by IV infusion over 2 hours ± 15 minutes.

Placebo is commercially available 0.9% sodium chloride sterile solution for injection. An equivalent volume (based on the volume required to give 10 mg/kg of PRV-3279) will be administered by IV infusion over 2 hours.

Body weight at time of randomization will be used for calculation of dose throughout the study.

Details of study drug administration will be provided in the pharmacy manual.

6.1.1. Monitoring for Infusion or Allergic Reactions

Infusion reactions or allergic reactions have been observed with administration of biologic therapies. Note that per Exclusion 12, study drug must not be administered to individuals with a known or suspected intolerance or hypersensitivity to any biologic medication or known allergies or clinically significant reactions to human proteins, to monoclonal antibodies or antibody fragments, or to any components of the PRV-3279 formulation used in this study.

Serious allergic reactions (e.g., anaphylaxis) may occur at any time during the administration of study drug. Serum sickness-like reactions (also known as delayed hypersensitivity reactions) have been observed 1 to 14 days after study drug administration. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgia, polyarthralgia, hand and facial edema, and/or dysphagia.

Examples of severe infusion reactions include symptomatic hypotension, symptomatic hypertension, bronchoconstriction/vasospasm, bronchospasm with wheezing, laryngeal/tracheal edema, laryngospasm, congestive heart failure, circulatory failure/cardiogenic shock, angioedema, urticaria (e.g., lip edema with associated bronchospasm), acute respiratory distress syndrome (e.g., new and rapid onset hypoxia, pulmonary infiltrates/edema on radiography, dyspnea requiring ventilator support), or symptomatic brady- or tachyarrhythmias.

Examples of non-severe reactions include asymptomatic hypotension, shortness of breath, rash, urticaria, flushing, chest pain, fever, back pain, peripheral edema of extremities, vasovagal reactions, chills/rigors, nausea/emesis, headache, diaphoresis, lightheadedness, somnolence, or myalgia.

A physician must be immediately available at the site at all times during the administration of study drug. All patients must be observed carefully for symptoms of an infusion reaction during the infusion and for 2 hours after the first IV infusion of study drug and at least 30 minutes at other visits. The Investigator should use clinical judgment in assessing the intensity of any infusion reactions. The examples given above are for guidance only. Infusion reactions may be considered either severe or non-severe depending on the clinical circumstance.

If a mild infusion reaction is observed, the Investigator should consider whether treatment such as oral paracetamol/acetaminophen and/or oral antihistamine should be given. In addition, the Investigator may elect to provide premedication for patients at subsequent visits, so long as no other contraindications are present.

The following precautions should be applied on dosing days:

- Before an infusion is started, the appropriate personnel, medications (e.g., epinephrine, inhaled β-agonists, antihistamines [may include H1 and/or H2 histamine receptor antagonists]), and corticosteroids), and other requirements to treat allergic reactions, including anaphylaxis, must be available. Clinical sites must have immediate access to a crash cart and electrical defibrillator.
- If a patient has a severe infusion reaction, the infusion should be stopped immediately, and the patient should be treated according to institutional guidelines. If a severe infusion reaction occurs, the patient should receive no further infusions of study drug (Section 7.1).
- Any adverse reaction during the infusion of study drug should be noted.

6.2. Preparation/Handling/Storage/Accountability

A Pharmacy Manual will be provided with complete details of preparation, handling, storage, and accountability. An overview is provided in this section.

PRV-3279 will be supplied by the Sponsor for use in this study. PRV-3279 will be shipped under cold-chain management to the study site and stored at 2-8ºC in light-proof containers. Under these conditions, the shelf life of PRV-3279 is 3 years.

Placebo (0.9% saline) will be supplied by the study sites.

Unblinded pharmacy personnel at each site will be responsible for drug storage, preparation, and dispensing according to the Pharmacy Manual. Unblinded pharmacy personnel will not be involved in any other aspect of the study and will not communicate study drug details to other blinded study personnel. Study drug will be prepared in a nature to ensure the blind is not broken. Timing of preparation and dispensing must be the same for both PRV-3279 and 0.9% saline (placebo should not be released until an equivalent time has passed for preparation of PRV-3279).

Proper aseptic techniques must be used when preparing and administering sterile parenteral products such as PRV-3279 and 0.9% sodium chloride. The study drug should be inspected visually for particulate matter prior to administration. If concerns regarding the quality or appearance of the investigational product arise, it must not be dispensed, and the Sponsor must be contacted immediately.

Study personnel should record and maintain shipping and receiving records of the study drug, and report to the Sponsor immediately any defect or issues with quality, quantity, or cold-chain shipping. The site will maintain accurate dosage preparation records and should ensure that all pertinent information on the preparation and dose administration is captured in source documents. Such information should be made available to the Sponsor's site monitoring representative(s) during monitoring visits.

Upon termination of the study, or at the request of the Sponsor, pharmacy personnel must return the remaining study drug to Sponsor, unless it is destroyed at the site as agreed upon by both the Sponsor and the site.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization

Enrolled patients meeting the eligibility criteria will be randomized in a 1:1 ratio to the PRV-3279 or placebo group. Randomization will be stratified by presence or absence of serum anti-dsDNA antibodies and, as available in certain geographies, the presence or absence of elevated [redacted] Stratified randomization will be generated electronically and transmitted to the site via an IVRS/IWRS.

Enrolled patients meeting the eligibility criteria will be assigned a unique screening number and randomization number to be used throughout the study.

6.3.2. Blinding

This study has a double-blind design. Treatment assignment records will be maintained by unblinded pharmacy personnel who must have no interactions with study patients and avoid disclosing treatment assignment to blinded personnel involved in the study conduct. In addition, some contract research organization (CRO) and Sponsor personnel and the IDMC members may be unblinded to provide necessary oversight.

All other study site staff, Medical Monitors, the CAC members, and Sponsor staff who interact with sites will be blinded to treatment assignment until the database lock.

Certain laboratory results will not be reported to Investigators or any other blinded study personnel during the study. These results may include serum total immunoglobulin levels, B lymphocyte stimulator (BLyS) levels, peripheral blood B cell levels, and B cell subsets (Stohl 2012b; Merrill 2018b; Merrill 2020).

Some markers that are known to be frequently and nonspecifically affected by improvement in SLE from any cause and/or by ongoing use of background treatments will not affect blinding and therefore will be reported to the site. Although differences in frequency of improvement may be discerned in treatment versus placebo groups, improvement often occurs and persists in placebo-treated patients or worsens in treatment groups in lupus trials, thus such patterns in an individual patient should not affect blinding. Such markers include results of hematologic and renal function tests and complement and anti-dsDNA antibody levels (Stohl 2012a; Merrill 2018b; Merrill 2019; Manzi 2012; Khamashta 2016), and other tests. Data from past trials confirm that these markers might change in both placebo and PRV-3279 treatment groups and may serve as a part of the disease activity assessments and as common warning signals of impending major organ flare. Thus, these test results can be disclosed to the Investigator during the study and may be useful for patient safety.

6.3.3. Emergency Unblinding

Blinding is critical to the integrity of this study. Every effort must be made to maintain the double-blind nature of the study. Therefore, emergency unblinding must only be done in the

event of a medical emergency or pregnancy, for which knowledge of the investigational product is deemed critical to the patient's management. If emergency unblinding is deemed critical to the patient's immediate management, a formal process is undertaken, and additional Sponsor and CRO personnel must be informed as soon as possible.

6.4. Study Treatment Compliance

Study drug will be administered on site by qualified personnel. If the full dose is not administered, this must be documented along with an explanation.

6.5. Dose Modification or Interruption

6.5.1. Treatment Modification

Treatment modifications (ie. change in study drug dose) are not permitted.

6.5.2. Treatment Interruption Rules

Study drug administration should be interrupted if any of the abnormal laboratory tests in Table 1 are reported. The patient should return for a repeat test as soon as possible. If the repeat test does not return to approximately the level at Screening and/or within normal reference limits before the next scheduled dose, the next dose should not be given.

Exceptions can be made at the Investigator's discretion, upon the approval of the Medical Monitor.

Table 1 Treatment Interruption Based on Safety Laboratory Tests

Variable	Level required at Screening	Level requiring treatment interruption	Next dose suspended
WBC	≥1.5 x 10^9/L	<1.0 x 10^9/L	No return to level required at Screening
Lymphocytes	≥0.3 x 10^9/L	<0.2 x 10^9/L	No return to level required at Screening
Neutrophils	≥1.0 x 10^9/L	<0.7 x 10^9/L	No return to level required at Screening
Platelets	≥40 x 10^9/L	≤30 x 10^9/L	No return to level required at Screening
Hemoglobin	>8.0 g/dL	<7.0 g/dL	No return to level required at Screening
ALT/AST	<2.5 x ULN	>3 x ULN	No return to level required at Screening
Serum creatinine	≤2 mg/dL	>2.5 mg/dL	No return to level required at Screening

6.6. Concomitant Therapy

The study personnel should record all dietary supplements (including vitamins and minerals), nutraceuticals, herbal medicines, traditional Chinese medicines, ayurvedic remedies, and any other prescription or nonprescription products taken by the patient from 3 months before Screening through the end of the study. The intake of such products must remain unchanged (except for permitted SLE medications [Section 6.6.2]) during the study unless a potential adverse reaction necessitates their discontinuation. Discontinuation of a concomitant medication must be discussed with the Investigator and the reason must be recorded.

6.6.1. Prohibited Medications

6.6.1.1. Prohibited Medications (See Exclusion Periods for Investigational and Biological Agents)

Use of any of the following medications or procedures are prohibited at entry:

- Plasmapheresis or plasma exchange
- Cyclophosphamide
- Investigational medications
- Any immunoglobulin therapies
- Biological immunomodulators, such as rituximab, belimumab

Mycophenolate mofetil, mycophenolic acid, JAK inhibitor, calcineurin inhibitors, azathioprine, and other oral DMARDs not specifically excluded prior to Screening, are permitted at Screening but must be discontinued prior to administration of study drug on Day 1.

6.6.1.2. Prohibited Medications at Any Time During the Study

Use of the medications listed below are prohibited at any time during the study (from study entry through the EOS visit).

Patients who receive the following medications will discontinue study drug but will be encouraged to remain in the study and continue all remaining assessments and procedures (Section 7.1):

- Plasmapheresis or plasma exchange
- Any immunoglobulin therapies
- Biological immunomodulators (rituximab and belimumab)
- Live vaccines

Patients will be permanently withdrawn from participation in the study (Section 7.2) if they receive an investigational medication.

6.6.2. Permitted SLE Medications

During the study period, hydroxychloroquine up to 400 mg per day (or other antimalarial [Section 10.5]) and/or prednisone up to 10 mg per day (or equivalent corticosteroid [Section 10.5]) may be continued. There are no restrictions on the use of NSAIDs or acetaminophen/paracetamol during the study except that on the morning of each visit, NSAIDs, acetaminophen/paracetamol, or any other analgesics should be avoided to allow proper evaluation of the patient's condition. The patient may re-start the NSAID or other analgesic after the study visit.

All other SLE treatments taken at the time of Screening will be withdrawn during the Screening period and prior to Randomization. (Refer to the exclusion criteria [Section 5.2] for restrictions to pre-screening treatment for SLE.)

6.6.3. SLE Medications to Treat a Flare

Treatment of a flare is not considered a protocol deviation. During the course of the study, when a patient meets the definition of a lupus flare (as defined in Section 1.1 and Section 3), the Investigator may prescribe any SLE medications, including increased doses of the permitted SLE medications (Section 6.6.2)..

If the patient initiates use of any SLE medications to treat a flare (or increases dose of the permitted SLE medications), the patient will discontinue study drug but will be encouraged to remain in the study and continue all remaining assessments and procedures (Section 7.1).

7. Discontinuation of Study Treatment and Patient Withdrawal

7.1. Discontinuation of Study Treatment

Every effort will be made to retain patients who permanently discontinue study drug during the study. All subsequent assessments should be performed as indicated in the SoA (Section 1.3).

Patients must discontinue the study drug for any of the following reasons:

1. A patient misses 2 consecutive doses or 3 or more total doses of the study drug for any reason.
2. Opportunistic systemic infection, or any infection which, in the opinion of the Investigator, puts patient at clinically significant risk from continued treatment with the study drug.
3. A severe allergic reaction or serum sickness that is considered to be related to the study drug.
4. A severe laboratory abnormality or severe TEAE or SAE that does not resolve before 2 consecutive doses or 3 or more total doses of the study drug are missed (see Section 6.5.2).
5. Use of SLE medication to treat a flare (Section 6.6.3) or use of prohibited medication (Section 6.6.1.2).
6. The decision of the Investigator, Medical Monitor, or Sponsor.

7.2. Patient Withdrawal from the Study

A patient will be withdrawn from study participation if any of the following conditions occur:

1. The patient withdraws consent.
2. The patient is unable to continue to provide consent.
3. The patient becomes pregnant.
4. The Investigator withdraws the patient from study participation.
5. The patient initiates use of an investigational medication other than PRV-3279 or placebo.

All patients who withdraw from study participation for any reason will be scheduled for an Early Termination visit (Section 1.3). If a patient withdraws the consent for the Early Termination visit or loses the ability to consent freely, no further treatment or assessments will be performed. A patient who withdraws due to pregnancy will be followed for the outcome of the pregnancy.

The reason for withdrawal must be documented in the case report form (CRF). Patients who withdraw prior to completing the Week 24 visit will be considered nonresponders in the primary and applicable secondary efficacy endpoints.

If a patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3. Lost to Follow-up

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

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

1. The site must attempt to contact the patient and reschedule the missed visit as soon as possible. The site must counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether the patient wishes to and/or should continue in the study.
2. Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
3. Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study. A certified letter will be sent to the patient's last known address to notify the patient of his or her termination from the study.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions will not be allowed. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct. Safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study intervention.

The maximum amount of blood collected from most patients over the duration of the study will not exceed 525 mL. Due to additional PK blood sample collections (Section 8.5) and Receptor Occupancy sample collections (Section 8.7), the maximum blood volume will be approximately 630 mL in approximately 30 patients.

8.1. Study Procedures

8.1.1. Screening Procedures

Screening evaluations must be completed and reviewed by the CAC to confirm that each patient meets all eligibility criteria. The Investigator will maintain a Screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable. Details of communication between the CAC and site Investigator are provided in the CAC charter.

At the Screening visit, SLE patients who present with active, moderate to severe symptoms will be invited to undertake screening procedures unless one or more exclusionary criteria are already identified.

Study-specific screening procedures will begin only after a properly conducted informed consent process. The following procedures will be completed during Screening:

- Patients will complete PRO questionnaires prior to any blood draws or other interventions with the study staff.
- A complete medical history will be obtained with a full review of systems. To the extent that a medical history was already obtained that day as a part of regular medical care, it need not be repeated.
- A complete physical examination will be performed (including weight and height). To the extent that a physical examination has already been performed on the same day by the study personnel as a part of regular medical care, aspects of the examination already performed need not be repeated.
- A preliminary review of inclusion and exclusion criteria based on available data. Pending data will be noted. Documented prior history of positive ANA must be obtained.
- Clinical disease activity measures will be completed by the Investigator. These will include the hSLEDAI (Furie 2011; Navarra 2011; Thanou 2014b) with SFI (Buyon 2005; Petri 2005), mSFI (Thanou 2014a), and ssPGA (Buyon 2005; Petri 2005), BILAG (Yee 2010), CLASI (Bonilla-Martinez 2008; Klein 2011), and tender and swollen joint counts (Sokka 2005).
- Screening blood tests will be drawn including hematology, serum chemistry, and coagulation panels, SLE serology tests, complement components C3 and C4, total serum

immunoglobulin levels, serum anti-dsDNA antibodies, HBV, HCV, and HIV serology, and PD markers. Samples for urinalysis and for serum pregnancy test (WOCBP) will also be obtained. Follicle stimulating hormone (FSH) and luteinizing hormone (LH) will be performed to confirm non-surgical menopause.

- An ECG must be completed and evaluated prior to randomization.
- Vital sign assessments after patient supine for at least 5 minutes.
- Record all dietary supplements (including vitamins and minerals), nutraceuticals, herbal medicines, traditional Chinese medicines, ayurvedic remedies, and any other nonprescription or prescription products taken by the patient within 3 months prior to Screening. (The list of such products should be reviewed by the Investigator before Randomization.)
- At the end of the Screening visit, if no exclusion criteria are known:
  - A patient will receive one or more IM injections of methylprednisolone acetate (Depo-Medrol® or equivalent) at a dose of ≥40 mg (maximum total dose 320 mg, maximum 4 injections). The dose will be determined by the Investigator to achieve a clinically significant improvement in SLE signs and symptoms that satisfy Inclusion 5b.
  - During the Screening period and prior to Randomization, patients must withdraw from all background treatments for SLE except the following medications:
    - Up to 10 mg prednisone (or equivalent corticosteroid [Section 10.5]) if taken for at least two weeks prior to Screening. Stable doses of prednisone of up to 15 mg may be tapered to 10 mg during the Screening period after giving the Depo Medrol injection(s).
    - Optional continuation of hydroxychloroquine up to 400 mg per day (or other antimalarial [Section 10.5]) that has been stable and well tolerated for a minimum of 2 months.
    - NSAIDs of any type, whether taken in regular doses or as needed (prior to the Randomization visit and any subsequent visits, patients will be reminded not to take NSAIDs on the day of all visits until the study procedures have been completed).

CAC Adjudication: During the Screening period, a history BILAG (list of all BILAG descriptors ever active in the patient), non-lupus medical history, age, weight, disease activity, along with a brief narrative written by the Investigator to summarize the patient's history of SLE features and current disease activity. This narrative should include past lupus manifestations, comorbid conditions, and a concise but clear description of the signs and symptoms that justify the disease activity scores. Information should be provided to convince the CAC that the patient is correctly diagnosed with SLE, has active features due to SLE that are significant enough to meet the study entry criteria, that the patient is stable enough to tolerate a withdrawal of background treatments while disease is ameliorated with temporary steroids, and there are limited or controlled co-morbidities, to suggest low risk of serious or opportunistic infections.

Once a patient has been deemed eligible to participate in the study, as adjudicated by the CAC, he/she may be scheduled for their Randomization visit. Prior to the Randomization visit (i.e., Day 1), all eligibility criteria must be confirmed by an Investigator.

8.1.2. Baseline/Randomization Visit (Week 0, Day 1)

Upon arrival at the clinic, patients will complete the PRO questionnaires prior to any blood draws or other interventions with the study staff. Patients will then have an interim history and a brief physical examination performed (including body weight). The Investigator will also complete the hSLEDAI, ssPGA, SFI, mSFI, BILAG, CLASI, and joint counts. To assess eligibility, the Investigator must confirm that the patient has achieved at least a moderate improvement in SLE signs and symptoms as indicated by:

CGIC score of "definite improvement" or "major or complete improvement"

AND

≥4-point decrease in hSLEDAI score from Screening, **OR** improvement by ≥1 severity grade in at least one BILAG system that was severe (A score) or moderate (B score) at Screening (i.e., from A to B-D or from B to C or D).

A pre-dose urinalysis and urine or serum pregnancy test (for WOCBP) will be obtained.

Vital signs, ECG, AE, and concomitant medication assessments will be performed.

Rapid COVID-19 test will be performed locally to confirm negative result prior to study drug administration.

Blood samples will be drawn for the following assessments at the time points specified in the SoA (Section 1.3): PK, PD and ADA, hematology, serum chemistry, and coagulation panels, total serum immunoglobulin levels, serum anti-dsDNA antibodies, complement components C3 and C4.

After confirmation of the eligibility criteria, patients will be randomly assigned 1:1 to treatment with either 10 mg/kg PRV-3279 or placebo via an IVRS/IWRS system.

The study drug will be administered at the study site. Patients will be observed for a minimum of 2 hours after end of the first infusion.

8.1.3. Scheduled Visits from Week 4 through Week 28

Study drug administration will take place at the study site every 4 weeks through Week 20 and study procedures performed as outlined in the SoA (Section 1.3). Patients will be observed for a minimum of 30 minutes after the end of each infusion.

At each visit, patients will also complete PRO questionnaires prior to any blood draws or other interventions with the study staff.

Rapid COVID-19 test will be performed locally to confirm negative result prior to study drug administration or other study assessments.

Patients will also undergo AE, concomitant medication, vital signs, ECG, and brief physical examination assessments (including body weight).

The Investigator will complete the hSLEDAI, ssPGA, SFI, mSFI, BILAG, CLASI, CGIC, and joint counts.

A pre-dose urinalysis dipstick and urine or serum pregnancy test (for WOCBP) will be obtained and resulted prior to study drug administration. Urine will also be sent to the central laboratory for urinalysis.

Blood samples will be drawn for the following assessments at the time points specified in the SoA (Section 1.3): PK, PD and ADA, hematology, serum chemistry, and coagulation panels, total serum immunoglobulin levels, serum anti-dsDNA antibodies, and complement components C3 and C4. (SLE serology test samples will be collected at Week 12 and Week 24 only.)

Patients will return at Week 28 for additional follow-up assessments per the SoA (Section 1.3) and to capture any potentially delayed AEs.

8.1.4. Unscheduled and "Flare Assessment" Visits

Patients should return to the study site for unscheduled visits if there are missed or repeated laboratory tests or AEs that require evaluation and/or treatment.

Patients should return for a Flare Assessment visit if they experience a known or suspected flare. The procedures for a Flare Assessment visit are listed in the SoA (Section 1.3).

The LFA international consensus definition of flare is as follows: "A flare is a measurable increase in disease activity in one or more organ systems involving new or worse clinical signs and symptoms and/or laboratory measurements. It must be considered clinically significant by the assessor and usually there would be at least consideration of change or an increase in treatment" (Ruperto 2011). The criteria of a flare, as defined in this study, are given in Section 1.1 and Section 3.

If a flare occurs, the patient may be treated as outlined in Section 6.6.3, and the patient will be considered a nonresponder in the primary and applicable secondary efficacy endpoints.

8.1.5. Efficacy Assessments

During the study per the SOA (Section 1.3), the disease activity of SLE and PROs will be evaluated using the following instruments:

Disease Activity Instruments: hSLEDAI, ssPGA, SFI, mSFI, BILAG Index, CGIC, CLASI, and tender and swollen joint count.

PROs: SF-36, FACIT--Fatigue scale, and PGIC and PGIS scales.

8.1.6. Disease Measurement Instruments

8.1.6.1. Hybrid Systemic Lupus Erythematosus Disease Activity Index (hSLEDAI)

The version to be used in this study will be the hSLEDAI which was employed to validate the SRI-4 outcome measure (Furie 2009). This is also the SLEDAI utilized in the successful Phase 3 trials for belimumab (Navarra 2011; Furie 2011; Stohl 2017; Zhang 2018; Tanaka 2019). The advantages of the hSLEDAI over other versions of the SLEDAI have been reviewed (Thanou 2014b; Merrill 2019). Although the differences are minor, the hSLEDAI corrected a major

inconsistency in the proteinuria definition of the original SLEDAI, as did the SLEDAI 2K (Gladman 2000). However, the SLEDAI 2K has a very low threshold for scoring arthritis, allowing patients with minimal disease to score 4 points, which can impair interpretation of both entry disease level and the improvement threshold (Merrill 2019). The hSLEDAI is therefore the preferred instrument both in terms of clinical face validity and in the interpretability of data from trials that have employed it.

The hSLEDAI is scored for disease activity present within the last 28 days, using history, physical examination and results of CBC, urinalysis, complement tests, and anti-dsDNA antibody testing (or additional confirmatory testing when scoring certain items as positive). The hSLEDAI scoring does not reflect symptom severity. One score is given for each sign or symptom that meets minimal criteria for the descriptor regardless of the degree of the manifestation. The numerical value of the score is based on the frequency and "usual severity" of each descriptor, which was derived through consensus of clinicians at the time the instrument was developed. As a result, the hSLEDAI is not very useful for comparing one patient to another and changes in mean/median hSLEDAI scores are not only difficult to interpret, as they may be misleading. However, because one or more symptoms must virtually disappear prior to any decrease in the score, the hSLEDAI has emerged as a relatively stringent and discriminatory endpoint for SLE trials when score decrease is incorporated as a dichotomous feature of endpoints. See Section 10.6.2.1 for the hSLEDAI form and glossary.

8.1.6.2. SELENA-SLEDAI Physicians Global Assessment (ssPGA)

This measure has the base of a visual analogue scale (VAS), but is anchored with cutoffs for mild, moderate and severe disease. The very far left end reflects complete remission. The very far right end indicates 'the most severe disease possible.' This does not mean only the most severe disease seen in a particular patient, but the most severe disease ever seen in all SLE patients. When scoring the ssPGA, the assessor should always consider the score from the previous visit, so that transitional scoring from month to month is consistent with changes in the patient's condition (Buyon 2005; Petri 2005). In the past the ssPGA has produced confusing results. This could be, in part, because the instructions for how to use the cutoffs were inconsistently taught by CROs. The Investigators be instructed in the correct and consistent use of the anchors in scoring this measurement, (e.g., mild disease will be scored between 0 and 1, moderate disease will be scored between 1 and 2 and severe disease will be scored between 2 and 3). Also, the original ssPGA instructions from the SELENA-SLEDAI group will be used in training as archived online in the LFA Professional Online Instrument Training site (https://www.LFA-POINT.org). See Section 10.6.2.3 for an example of the ssPGA VAS.

8.1.6.3. SELENA-SLEDAI Flare Index (SFI)

This index is used with all versions of the SLEDAI and incorporates changes in scoring of the main SLEDAI form, changes in ssPGA scoring, medication changes, and assessment of new or worsening descriptive features of active SLE. Flares are designated as either mild/moderate or severe based on a combination of these factors (Buyon 2005; Petri 2005). We will collect information using this original, widely used SFI for the main analyses, but we will also collect data in an exploratory endpoint from a modified version (mSFI, see below).

8.1.6.4. Modified SELENA-SLEDAI Flare Index (mSFI)

This modified version of the SFI removes the restrictive and outdated medication rules and one extra data point is collected by asking the Investigator to distinguish (by clinical opinion) between mild and moderate flares. The mSFI was shown to better approximate the clinician's opinion on whether or not there is a flare (Thanou 2014a), and it was found that many features that meet criteria for mild/moderate flare are determined by physicians to be clinically insignificant. The mSFI will be evaluated in this trial as an exploratory evaluation to enable an assessment of only moderate and severe flares, which is expected to be more discriminatory between an effective treatment and placebo than when mild, clinically insignificant flares are included. This possibility will be examined by direct comparison to the original SFI, and BILAG Flare definitions. The mSFI requires no extra data collection other than for the Investigator to provide a simple distinction between mild and moderate flares by checking a box to distinguish the severity.

8.1.6.5. British Isles Lupus Assessment Group (BILAG) Index

This instrument is scored for disease activity present within the last month using history, physical examination and results of CBC, general chemistry panel, and urinalysis. Additional testing is required for scoring certain items, but only if clinically warranted. The BILAG is a transitional index, thus clinical progress between visits is an integral part of the scoring algorithm. The instrument consists of 97 descriptors for signs and symptoms of lupus divided into 9 organ systems (see Section 10.6.2.4 for forms, glossary and scoring rules). At consecutive visits, each organ system receives a rating of A (severe disease activity), B (moderate disease activity), C (mild disease activity), D (no disease activity in an organ previously affected) or E (organ inactive and never previously active). These ratings are derived from assessments made on each descriptor within each organ and the determination of whether activity is not present, improving, same, worsening or new/recurrent when comparing the degree of disease during the past month to the previous month (Yee 2010).

8.1.6.6. Cutaneous Lupus Erythematous Disease Area and Severity Index (CLASI)

This evaluation is scored predominantly with objective findings observed in the mucocutaneous system on the day of the visit. Disease areas are defined (and to some extent weighted) by the most characteristic locations of lupus rash. In each area the most severe lesion is rated for color and associated features of severity such as scaling and hypertrophy. Because of this, most active, discoid lesions are likely to receive a higher score than subacute or acute cutaneous lupus that might cover an equivalent area, which is appropriate (Bonilla-Martinez 2008; Klein 2011). See Section 10.6.2.6 for the form and CLASI form.

8.1.6.7. Tender and Swollen Joint Counts

This will be performed by accepted methods employed in studies of rheumatoid arthritis (Sokka 2005). Using the identical techniques, tender and swollen joint counts have been successful at discriminating treatment from placebo in several lupus studies as well (Furie 2017; Merrill 2017; Khamashta 2016). For this study, the 28-joint count will be used. The site staff member assigned to perform these counts will receive training in joint assessment prior to the study. See Section 10.6.2.7 for the tender and swollen joint counts form.

8.1.7. Patient-Reported Outcomes

Multiple semi-structured interviews were conducted with 10 SLE patients (Askanase 2019a) in order to better understand the kinds of lupus symptoms experienced from the patients' point of view, and the impact of lupus features on daily function and quality of life. Symptoms that were of most concern to the patients were arthritis (reported spontaneously by 100%), and fatigue (also reported by 100%, half spontaneously and have elicited). The following were noted by at least 50% of the patients: swelling (90%), weakness (90%), difficulty breathing/shortness of breath (80%), skin problems (80%), chest pain (70%), hair loss (60%), muscle pain, aching, or stiffness (50%), and fever (50%).

Problems that lupus patients experience extend beyond their physical well-being, as found in a different qualitative research report (Leung 2019). Patients reported a burden of ambiguity, inconsistency, and lack of symptom predictability, poor communication with family/friends/partners, and health care providers and lack of external validation for patients' experiences (appraisal support). During structured interviews and a focus group, these social themes were expanded, finding a significant impact of SLE on interpersonal, familial and romantic relationships. The unpredictability of symptoms was highlighted along with lack of empathy by physicians and clinic staff and this was thought to affect correct diagnosis and appropriate follow-up care. Fatigue was reported as a major clinical feature in these interviews and the presence of pain was stressed, along with difficulties in communicating the pain to healthcare providers and others.

The extensive paperwork involved in trial participation is considered a significant burden to patients who have experienced trial participation (Arriens 2020). Nevertheless, lupus patients have a good knowledge base and strong interest in participation in trials for reasons that include altruism and the potential for personal benefit. Consistent with the reports above, other burdens of trial participation were the uncertainties, potential disappointments and the difficulties maintaining life-health balance. The PROs intended for the current study will all have a one-month recall period and are likely to require less than 30 minutes each month from a patient. At the end of the trial, patients will be given a questionnaire to determine how burdensome this was perceived to be and whether certain PROs (or sections of PROs) were perceived to be more or less relevant to their experience.

The SF-36 measures QOL and physical function and symptoms. The FACIT-Fatigue scale focuses more in depth on fatigue and the different contexts in which it occurs, resulting in more contextual information about this singular major disabling feature of SLE than the SF-36 can provide. The PGIS and PGIC are simple, rapid anchoring assessments that are very user friendly and can help to verify the findings of how disease severity and disease change may be affecting various items on the QOL and PRO disease activity measures. They are different from each other because one measures severity and the other change from the last visit.

8.1.7.1. Short Form 36 Health Survey (SF-36)

The Short Form 36 (SF-36) Health Survey (Ware 1992) is one of the most widely used PROs currently used in SLE (Bangert 2019) Within a limited number of questions, it captures eight domains relevant to QOL: (physical functioning, general health, mental health, vitality, role physical, role emotional, bodily pain, and social functioning) and provides two summary scores (PCS and mental component score [MCS]. Scoring can range from 0 to 100 with higher scores

designating better health. The psychometric measurement properties of this instrument have been extensively studied and applied for lupus across multiple cultures and languages. Reliability, including internal consistency and test-retest reliability; validity; and responsiveness of SF-36 have been confirmed for SLE (Baba 2018; Devilliers 2015; Garcia-Carrasco 2012; Nantes 2018; Strand 2003; Strand 2014; Strand 2020; Thumboo 2000; Touma 2011; Yilmaz-Oner 2016). See Section 10.7.1 for an example of the SF-36.

The potential importance of obtaining patient reports using the SF-36 is underscored by the findings of one study that both the SF-36 physical component subscale score and self-rated health were associated with mortality (Azizoddin 2019). However, when considering the use of PROs in time-limited interventional trials, the concept of Minimally Clinically Important Differences (MCIDs) is central to the interpretation of these instruments (Rai 2015). A clinical intervention can be interpreted as clinically meaningful if the score change that occurs when it is tested exceeds the validated MCID for that disease (Rai 2015). MCIDs have been established for the SF-36 in SLE (Strand 2003; Strand 2014). For PCS and MCS, ≥2.5 point increases in the score meet the MCID for improvement and ≥-0.8 decreases meet the threshold for clinically significant worsening. For individual domain scores, ≥5.0 point increases indicate clinically significant improvement and ≥–2.5 decreases reach MCID for worsening. These MCID values were used to evaluate SF-36 results in a combined analysis of two phase 3 trials of belimumab in SLE (Furie 2014). At Week 52 mean improvements in SF-36 PCS were greater in SRI-4 responders when compared to nonresponders and exceeded the MCID. Not all SF-36 individual domains gave consistent results between the two belimumab trials, suggesting the importance of exploring the aspects of disease that do or do not improve from the patients' point of view (Furie 2014; Strand 2019). It is possible that the SF-36 may lack key domains that are particularly relevant to a population with SLE, including fatigue (Moses 2005). PGIC and PGIS will also be used to assess MCIDs in the efficacy instruments.

8.1.7.2. Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)

Fatigue is reported by most patients with SLE and is one of its most disabling symptoms (Lateef 2012; Fonseca 2014; Gordon 2013; Holloway 2014; Elefante 2020) and although it is known to be multifactorial it cannot be completely explained by depression or other mood disorders (Fonseca 2014). In an online survey of 21,101 patients with self-reported lupus, fatigue, pain, and joint pain were rated as moderate or severe by at least 80% of patients who reported these symptoms (Nyman 2020). Although cross sectional comparisons of fatigue to disease activity have not shown a reliable relationship, it has been found that as patients objective disease activity improves and remains stable over time, fatigue has been documented to improve as well (Strand 2019), making a thorough understanding of types of fatigue in SLE important to measure in clinical trials. A dedicated instrument to sort out the components and elements of fatigue is of value in clinical trials.

The FACIT-Fatigue Scale (Cella 2002) is a questionnaire that evaluates both physical and mental fatigue and how fatigue affects function and activities of daily life. Thirteen items are each scored on a four-point scale with lower scores reflecting more fatigue. The FACIT-F was first validated for rheumatic diseases in 1997 (Yellen 1997) and has since been applied in several SLE studies (Furie 2014; Strand 2019; Elefante 2020). Psychometric properties have been established, including content validity (Kosinski 2013), reliability (Lai 2011), validity (Goligher

2008; Lai 2011), and responsiveness (Furie 2014). In the SLE population, the instrument's ability to detect change over time has been critically reviewed (Kwan 2017) and found to be meaningful. The median FACIT-F score in a lupus population has been reported to be lower than that of healthy controls and not influenced by age, SLE disease duration, cross-sectional disease activity scores or accumulated organ damage (Elefante 2020). FACIT-F scores demonstrated a significant correlation with other PROs including the SF-36 but may be confounded by the presence of fibromyalgia (Elefante 2020). Fatigue is very likely multifactorial in lupus patients but the FACIT-Fatigue score has been demonstrated to improve along with treatment that was determined to be clinically efficacious for SLE disease activity by physician outcome assessments (Stohl 2017; Furie 2014). See Section 10.7.3 for an example of the FACIT-F.

In a combined analysis of two Phase 3 trials of belimumab in SLE, SRI-4 responders had higher mean improvements in FACIT-Fatigue scores compared to nonresponders and only the responders met the MCID cutoff (Furie 2014), suggesting that this patient-reported endpoint has at least the potential to show consistency with physician-recorded disease improvement. Both belimumab treatment dosing groups had significant improvements in FACIT-Fatigue by Week 52 compared to placebo. Improvements were observed after 8 weeks of treatment and persisted throughout the trial. In a different belimumab trial in lupus patients (Stohl 2017) improvement in FACIT-Fatigue was only found in a post-hoc subgroup analyses in Hispanic or Latino patients. Long term improvement in fatigue, however, was reported in a 6-year follow-up study of belimumab in SLE (Strand 2019).

8.1.7.3. Patient Global Impression Scales (PGIS and PGIC)

The SF-36 and FACIT-Fatigue Scales have established MCID but the other exploratory endpoints to be studied in this trial do not. To provide evidence that may help interpret a meaningful within-patient score change in these newer instruments, simple discontinuous scales will be administered for PGIS and PGIC. These have evolved as the PRO counterpart to the Clinical Global Impressions scale (CGI), which was developed in 1976 by the National Institute of Mental Health (US) and are widely accepted in clinical studies of a wide variety of disorders and have been translated into many languages (Kroenke 2019; Le Gal 2010). These anchor scales will be administered such that, like all of the other PROs used in this study, they have a recall period of one month and will be completed after, the other PRO instruments. Please see Section 10.7.2 for examples of these anchor scales.

8.1.8. Laboratory Tests of Lupus Disease Activity

The activities of SLE will also be assessed by analyzing the levels of serum anti-dsDNA antibodies, complement components C3 and C4, and total serum immunoglobulin levels (IgG, IgM, IgA, IgE) in blood samples obtained at the visits outlined in the SoA (Section 1.3). Additional autoantibodies to be analyzed include Sm, RNP, anti-cardiolipin antibodies (IgA, IgG, IgM), anti-beta 2 glycoprotein (GPI) antibodies (IgA, IgG, IgM), and the lupus anticoagulant.

8.2. Safety Assessments

Safety assessments to be conducted at each monthly visit are listed in the SoA (Section 1.3).

If an unscheduled visit occurs, safety assessments should be conducted in the same way as a scheduled visit.

8.2.1. Physical Examinations

A complete physical examination will be performed at Screening and includes, at a minimum, assessments of the head, eyes, ears, nose, throat, skin, cardiovascular, respiratory, mucocutaneous, musculoskeletal, lymphatic, gastrointestinal, and neurological systems. Gynecologic, breast, and rectal examinations are not routinely required except to address a specific medical issue.

A brief physical examination will be performed at time points noted in the SoA (Section 1.3). The brief physical examination will include, at a minimum, assessments of the mucocutaneous, respiratory, cardiovascular, gastrointestinal, and musculoskeletal as well as any other organ/system suggested by the interim history.

Height will be measured recorded at Screening, and weight will be measured and recorded at each visit.

8.2.2. Vital Signs

Vital signs will be obtained at time points noted in the SoA (Section 1.3). Vital signs should be assessed after the patient has been supine for at least 5 minutes and will include body temperature, heart rate, respiratory rate, and blood pressure. On dosing days, vital signs should be performed once during the 30 minutes before the study drug infusion and again approximately 30 minutes after the end of infusion. Abnormal and clinically significant vital signs should be noted as AEs by the Investigator.

8.2.3. Electrocardiograms

A 12-lead ECG will be obtained at time points noted in the SoA (Section 1.3), using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QT interval corrected for heart rate using Friderica's cubed root formula (QTcF) intervals. Additional ECGs may be performed as needed. The Investigator should report one of the following: normal, abnormal not clinically significant, abnormal clinically significant.

8.2.4. Tuberculosis Screening

See Exclusion 20 for eligibility criteria regarding TB Screening. Indeterminate tests should be repeated. If the repeat test is positive or still indeterminant, the patient is excluded (repeat QuantiFERON tests may be performed locally).

8.2.5. Clinical Safety Laboratory Assessments

Clinical safety laboratory tests are listed in Section 10.2 and will be performed at time points outlined in the SoA (Section 1.3).

Hematology includes CBC will differential: hematocrit, hemoglobin, red blood cell (RBC) count, red blood cell distribution width (RDW), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelets, absolute

reticulocyte count, WBC count with absolute counts of neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

Serum chemistry includes sodium, potassium, chloride, alkaline phosphatase (ALP), ALT, AST, blood urea nitrogen (BUN), creatinine, CPK total protein, albumin, glucose, calcium, phosphorous, and bicarbonate.

Coagulation panel: prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), and fibrinogen.

TBNK panel is a quantitative lymphocyte panel that includes the assessment of CD4+ T cells, CD8+ T cells, B cells, and natural killer (NK) cells.

Serum pregnancy test will be performed during Screening for WOCBP. FSH and LH will be performed during Screening to confirm non-surgical menopause. A urine or serum pregnancy test will be performed before each dose of study drug for WOCBP.

A negative rapid COVID-19 test is required before administering each dose of study drug.

A urinalysis will be performed at all study visits.

Out of range laboratory tests are not necessarily an AE. The following laboratory abnormalities should be documented and reported as AEs:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the patient to have study drug discontinued or interrupted.
- Any laboratory abnormality that required the patient to receive specific corrective therapy.
- If the laboratory test is indicative of a disease or infection, the disease TEAE term should be used.

8.2.6. Data Review Committees

8.2.6.1. Central Adjudication Committee (CAC)

The CAC responsibilities include:

- Confirm patients' eligibility to enter the study
- Adjudicate SLE flare
- Ensure the accuracy and consistency of scoring on the disease activity instruments

The CAC will be blinded to the study treatment. Details will be provided in the CAC charter.

8.2.6.2. Independent Data Monitoring Committee (IDMC)

An independent external committee consisting of 2 physicians and one statistician will be formed. Additionally, 1 to 2 external non-voting advisors with experience in rheumatology, infectious disease, cardiology and/or hematology may be added as needed. Meetings will be held approximately quarterly and as needed to review unblinded safety and other relevant data. After each meeting, the IDMC will make recommendations regarding study conduct. The IDMC may

recommend the continuation of the study with or without modifications, suspension, or termination.

Details will be provided in the IDMC charter.

8.3. Adverse Events (AEs) and Serious Adverse Events (SAEs)

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. Details are provided below as well as in Section 10.3.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the time of the signing of the ICF through the EOS at the time points specified in the SoA (Section 1.3).

TEAEs and treatment-emergent SAEs are defined as events that occur after the start of the study treatment. TEAEs and AEs occurring before the start of the study treatment will be reported separately.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours from the time the site becomes aware of it. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient 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 must promptly notify the Sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (see Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that ethical responsibilities towards the safety of patients and the safety of a study intervention under clinical investigation and legal obligations and 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, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

Details of all pregnancies in female patients and female partners of male patients will be collected from the start of study treatment through the safety follow-up visit.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as TEAEs

Disease flares of lupus will not be captured as AEs since they are an endpoint of the study. However, if they meet the criteria for an SAE such as a particularly severe flare, a life-threatening event or require hospitalization, it will be captured as an SAE regardless of causality.

8.3.7. Adverse Events of Special Interest

Adverse events of special interests (AESIs) are TEAEs, including SAEs, that are of scientific and medical concern specific to PRV-3279, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is considered appropriate.

The following AEs are considered AESIs:

- severe infections requiring IV antibiotics/antifungal/antiviral and/or hospitalization
- opportunistic infections related to immune suppression (e.g. pneumocystis carinii etc.)
- herpes zoster
- moderate or severe infusion site reactions
- anaphylaxis or severe hypersensitivity reaction
- new malignancy
- thrombosis
- MACE (Major Adverse Cardiovascular Events), defined as the composite of total death; myocardial infarction; stroke, hospitalization because of heart failure; and

revascularization, including percutaneous coronary intervention, and coronary artery bypass graft.

8.3.8. Infusion or Allergic Reactions

Please refer to Section 6.1.1.

8.4. Overdose

An overdose is defined as the accidental or intentional administration of any dose of the study drug that is considered both excessive and medically important. All occurrences of overdose must be reported to pharmacovigilance as an Other Reportable Event.

8.5. Pharmacokinetic Assessments

At all sites, PK samples will be collected at each visit within 30 minutes pre-dose and within 5 minutes after the end of infusion, any Flare Assessment visit due to immune-related AEs and at the follow-up visit. For approximately 30 patients, additional PK samples may be collected on Day 1 and Day 141 at 24 ± 4 hours, 48 ± 4 hours, 72± 4 hours, 168 ± 48 hours and 336 ± 48 hours post-dose. Detailed instructions on the collection, handling, and shipment of biological samples will be provided in the Laboratory Manual.

Serum samples will be analyzed to determine concentrations of PRV-3279 using a validated, specific, and sensitive immunoassay method.

8.6. Immunogenicity Assessments

Blood samples for ADA titers will be collected pre-dose on Day 1 as a control for natural ADAs in SLE, so that placebo patients with positive reactivity can be interpreted. ADA samples will also be collected at visits outlined in the SoA (Section 1.3) and at any Flare Assessment visit triggered by suspected immunologically related AEs. Detailed instructions on the collection, handling, and shipment of biological samples will be provided in the Laboratory Manual.

Titers of anti-PRV-3279 ADA will be analyzed using a validated immunoassay method.

8.7. Pharmacodynamic/Biomarker Assessments

Blood samples for PD markers will be collected at the visits outlined in the SoA (Section 1.3). (Note that for receptor occupancy assays (if performed), blood collections will only be conducted in select patients.) Blood samples will also be collected at any Flare Assessment visit allow the assessment of immunologic consequences of any suspected immunologically related AEs or flare. Detailed instructions on the collection, handling, and shipment of biological samples will be provided in the Laboratory Manual.

Analyses may include but are not limited to [redacted], B cell immunophenotyping, [redacted] assays, mRNA analysis including CD32B polymorphisms, and other exploratory serum markers. Phenotypic patterns may be evaluated by upregulated or downregulated cytokines and/or gene expression modules, as defined by the NIAID Human Immune Phenotyping Consortium to enable designation of each patient to one of seven known

SLE immunophenotype clusters derived from Random Forest Modeling of gene and cluster expression patterns (Guthridge 2020; Banchereau 2016).

Additionally, the underlying variables that may affect the impact of PRV-3279 on B cells will be explored. These will be compared between patients on PRV-3279 and placebo and between responders and nonresponders.

9. Statistical Considerations

9.1. Sample Size Determination

The published data from the Phase 2, double-blind, randomized, placebo-controlled study of a reversible B cell inhibitor, XmAb®5871, in SLE showed that the response rates of the maintenance improvement in SLE signs and symptoms in the intent-to-treat (ITT) population were 40.4% vs 23.1% at Day 225 and 57.7% vs 34.6% at Day 169 for the active arm and control arm, respectively (Merrill 2018d).[redacted]

9.2. Populations for Analyses

The analysis sets are defined as follows:

1. All Screened (ALL) analysis set

   The ALL analysis set consists of all Screened patients.

2. Full analysis set (FAS)

   The FAS analysis set includes all randomized patients who received at least 1 dose of study drug. Patients will be analyzed according to the randomized treatment. The analysis of efficacy endpoints will be performed in the FAS.

3. Per-Protocol (PP) analysis set

   The PP analysis set includes all FAS patients except those who have met the major protocol deviation criteria that are considered likely to affect the evaluation of the efficacy endpoints. These criteria will be defined, and the patients excluded from the PP analysis set will be identified and documented prior to unblinding of the study. The analysis of the primary efficacy endpoint will be performed in the PP set, if the PP analysis set differs substantially from the FAS.

4. Safety analysis set

   The safety analysis set includes all patients who take at least 1 dose of the study drug post-randomization. Patients will be analyzed according to the treatment actually received.

5. PK analysis set

   The PK analysis set includes all randomized patients who received at least 1 dose of the study drug and have at least 1 post-dose evaluable PK assessment.

6. Immunogenicity (IMG) analysis set

   The IMG analysis set includes all randomized patients who received at least 1 dose of the study drug and have at least 1 post-dose evaluable IMG assessment.

7. PD analysis set

   The PD analysis set includes all randomized patients who received at least 1 dose of the study drug and have at least 1 post-dose evaluable PD assessment.

9.3. Statistical Analyses

A detailed description of the statistical analyses, data derivation rules and handling of missing data, if any, will be provided in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to database lock and unblinding. This section briefly outlines the planned statistical analyses of the efficacy, safety, immunogenicity, PK, and PD.

9.3.1. General Considerations

All continuous endpoints and respective changes from baseline (absolute and percent) will be summarized (N, mean, median, standard deviation [SD], minimum and maximum). Rates or proportions will be tabulated by frequency of occurrence (count) and percent. All summaries will be by treatment and collection time.

Baseline values will be derived from observations collected prior to study drug administration.

All the statistical analyses for the clinical efficacy and safety assessments will be performed using SAS version 9.4 or above.

9.3.1.1. Handling of Missing Data

The rules for handling missing data will be provided in detail in the SAP.

9.3.2. Primary Analysis

The primary endpoint is proportion of patients who maintain the improvement in SLE disease activity from Baseline (Day 1) to Week 24, defined as no lupus flare during this period, who have not missed 2 consecutive doses or 3 or more total doses of the study drug for any reason, who have not taken a new SLE medication, and whose dose of SLE medication has not been increased.

The null hypothesis is that the proportion of patients who maintain improvement through Week 24 (i.e., responders) in the PRV-3279 group is the same as that in the placebo group. The alternative hypothesis is that the proportion of patients who maintain improvement through Week 24 in PRV-3279 group is different from that in the placebo group.

The difference in the proportion of patients who maintain improvement between the PRV-3279 and the placebo arms will be tested using the Cochran-Mantel-Haenszel (CMH) test, accounting for randomization stratification factors. This will be tested at two-sided 0.20 level of significance. If the data is sparse that the asymptotic statistical test is inappropriate, the Fisher's Exact test will be used instead. The numbers and percentages of responders and the associated

80% confidence interval (CI), and the proportion difference and the associated 80% CI between treatment groups will be tabulated by the treatment group.

The primary analysis will be conducted on the FAS population. Analysis of the primary endpoint will also be conducted on the PP populations if PP population differs substantially from the FAS population.

9.3.3. Secondary Efficacy Analysis

All secondary efficacy analyses will be conducted on the FAS and summarized. The statistical testing on the secondary endpoints will not be adjusted for multiplicity and will be considered descriptive and non-inferential. The secondary efficacy analyses are:

1. The time to treatment failure will be summarized by treatment group using Kaplan-Meier analysis (median, 95% CI, number of events, number censored, etc.) and Kaplan-Meier plots. The stratified log-rank test will be used to test for difference between treatment groups.
2. The proportion of patients who achieve the EULAR-recommended goal of low disease at Week 24 will be compared between the groups using the same test as the primary efficacy analysis.
3. The change from Screening to Week 24 in the SF-36 PCS will be analyzed using the Mixed Model for Repeated Measurements (MMRM). The model will include treatment, visit, randomization stratification factors, baseline score as fixed effects, and the treatment by visit as interaction term.
4. The proportion of patients who achieve SRI-4 at Week 24 will be compared between the groups using the same test as the primary efficacy analysis.
5. The proportions of patients who meet the BICLA criteria at Week 24 will be compared between the groups using the same test as the primary efficacy analysis.

The time to treatment failure in subgroups by stratification will be summarized by treatment using the Kaplan-Meier method and compared between treatment groups using the log-rank test.

9.3.4. Exploratory Analyses

Details of the exploratory analyses will be provided in the SAP.

9.3.5. Safety Analyses

All safety analyses will be conducted on the Safety analysis set.

The safety variables, including AEs (coded using the Medical Dictionary for Regulatory Activities [MedDRA]) will be tabulated by actual treatment received. TEAEs, TEAEs leading to withdrawal, treatment-emergent SAEs, and AESIs will be tabulated by MedDRA system organ class and preferred term and treatment group. Potentially clinically important (PCI) laboratory tests and abnormal and clinically significant vital signs will be tabulated and listed by visit and treatment group. Similarly, abnormal and clinically significant ECG findings will be listed by visit and treatment group and tabulated by treatment group.

9.3.6. Immunogenicity Analyses

The incidence and titers of positive ADAs will be tabulated. The potential association of immunogenicity with safety, PK, and PD results will be explored graphically. The PK, PD, and immunogenicity populations will be used for these assessments.

9.3.7. Pharmacokinetic

In all patients, PRV-3279 serum concentration collected at pre-dose and post-end of infusion on Weeks 0, 4, 8, 12, 16, 20, 24 and 28 will be tabulated by time point using descriptive statistics and listed.

Individual PRV-3279 concentrations will be listed and summarized and graphically presented by scheduled time point. The following descriptive statistics will be presented for serum concentrations obtained at each nominal time point: n, mean, SD, percent coefficient of variation (CV%), GM, geometric CV% (gCV%), median, minimum, and maximum values.

For all patients, PRV-3279 serum concentration will be collected within 30 minutes pre-dose and within 5 minutes after the end of infusion in order to determine the accumulation of multiple infusions and steady-state serum concentration.

For approximately 30 patients, extensive PK sampling may be conducted on Day 1 and Day 141. The PK parameters listed in Table 2 will be calculated based on actual sampling times using noncompartmental analysis methods. Summary statistics will be tabulated for serum PK parameters by Day. Descriptive statistics for calculated PK parameters include n, arithmetic mean, SD, CV%, GM, gCV%, median, minimum, and maximum values. For T_{max}, only median, minimum, and maximum values will be presented.

Table 2 Pharmacokinetic Parameter Definitions

Parameter	Definition	Time Point
C_{max}	Maximum serum concentration determined directly from the concentration-time profile	Day 1, Day [redacted]
C_{trough}	Serum concentration at pre-dose	Day 1, Day [redacted]
T_{max}	Time of maximum serum concentration determined directly from the concentration-time profile	Day 1, Day [redacted]
[redacted]	[redacted]	Day 1, Day [redacted]
AUC_{0-t}	Area under the concentration-time curve from pre-dose (time 0) to the time of the last quantifiable concentration (t_{last})	Day 1, Day [redacted]
[redacted]	[redacted]	Day 1 [redacted]
$t_{1/2}$	Terminal elimination half-life calculated as: ln2/λz	Day 1, Day [redacted]
CL	Clearance	Day 1, Day [redacted]
V_d	Volume of distribution in terminal phase	Day 1, Day [redacted]
V_{ss}	Volume of distribution at steady state	Day 1, Day [redacted]

Parameter	Definition	Time Point
MRT	Mean Residence Time	Day 1, [redacted]
RacC_{max}	Accumulation ratio, C_{max} on Day[redacted]/C_{max} on Day 1	N/A
RacAUC	Accumulation ratio, AUC_{0-}[redacted] on Day [redacted]/AUC[redacted] on Day 1	N/A

9.3.8. Pharmacodynamic Analyses

Changes in individual biomarkers from baseline to the selected posttreatment time points will be summarized. Associations between baseline levels and changes from baseline in select biomarkers and clinical response will be explored. The biomarker analysis will characterize the response of patients to PRV-3279 and loss of response, to determine if response to PRV-3279 can be predicted and to further our understanding of lupus.

The relationship between serum concentrations of PRV-3279 and PD and/or clinical endpoints will be graphically explored and if warranted further elucidated with appropriate modeling techniques.

9.3.9. Subgroup Analyses of Primary/Secondary Efficacy Endpoints

Subgroup analysis may be conducted on the primary endpoint for each level of randomization stratification factors and relevant demographic and baseline characteristics, such as age group, race, baseline disease status, etc. The details of the subgroup analyses will be provided in the SAP.

9.3.10. Sensitivity Analyses

Sensitivity analysis may be conducted on primary endpoint if intercurrent events are identified during the course of treatment. Probable intercurrent events and sensitivity analyses will be provided in detail in the SAP.

9.4. Interim Analysis

No interim analysis is planned.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the

requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a patient's agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will not provide this separate signature.

10.1.4. Data Protection

Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the ICF.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the Investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the institution and the Sponsor or their designee.

10.1.6. Data Quality Assurance

All relevant patient data relating to the study will be recorded on the CRF and/or handheld devices unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

Study monitors will perform ongoing source data verification to confirm that data collected and/or entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7. Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of patients.

The first act of recruitment is the first patient Screened and will be the study start date.

The Sponsor or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- 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 patients by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

10.2. Appendix 2: Clinical Laboratory Tests

Except where noted, safety laboratory tests will be performed by central laboratories. Procedures for collecting, processing, and shipping blood samples will be detailed in the Laboratory Manual.

The following clinical laboratory tests conducted at Screening only:

- Serum pregnancy test for WOCBP
- Serum FSH and LH to confirm non-surgical menopause
- HBsAg, HBsAb, total HBcAb (IgM and IgG), HBV DNA (if HBcAb is positive), HCV RNA
- HIV 1 &2 (and HIV confirmation, if applicable)
- QuantiFERON Gold TB test (local testing may be allowed in a case-by-case basis such as to repeat an indeterminate initial test result)

The following clinical laboratory tests will be performed at the time points outlined in the SoA (Section 1.3).

- Hematology: hematocrit, hemoglobin, RBC, RDW, MCV, MCH, MCHC, platelets, absolute reticulocyte count, WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) including absolute neutrophils, lymphocytes, and eosinophil count.
- Chemistry: sodium, potassium, chloride, calcium, ALP, ALT, AST, BUN, creatinine, CPK, direct and total bilirubin, total protein, albumin, glucose, phosphorous, and bicarbonate.
- Coagulation Panel: PT/INR, aPTT and fibrinogen
- Urinalysis
- SLE Serology: ANA, ENA (including anti-SSA, anti-SSB, anti-Sm, anti-RNP), anti-cardiolipin antibodies, anti-beta 2 GPI antibodies, and the lupus anticoagulant
- SLE Disease Activity Markers: serum anti-dsDNA antibodies, complement components C3 and C4, and total serum immunoglobulin profile including IgG, IgA, IgM, and IgE
- TBNK panel: CD4+ T cells, CD8+ T cells, B cells, NK cells (Quantitative Lymphocyte Subset Panel)

A urine or serum pregnancy test for WOCBP will be performed before each dose by the local laboratories.

Rapid tests for SARS-CoV-2 (COVID-19) will be performed locally during Screening and confirmed negative before each dose.

Additional blood samples for PK, immunogenicity, and PD will be collected as outlined in Section 8.5, Section 8.6, and Section 8.7, respectively.

Note that some parameters will not be reported to study sites during the study to maintain the double-blind nature of the study (Section 6.3.2).

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study patient, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: 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.
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, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • 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. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • 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.

10.3.2. Definition of SAE

If an event is not an AE per 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).

An 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 refers to an event in which the patient 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 patient 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 fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
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 should 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 patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered 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.

10.3.3. 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 will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the Investigator to send photocopies of the patient's medical records to the Sponsor and/or CRO in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor and/or CRO. In this case, all patient identifiers, except the patient number, will be redacted on the copies of the medical records before submission.
- The Investigator will 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) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for 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 patient, 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. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- 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 will 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 will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (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 has provided an assessment of causality.
- The Investigator may change his/her opinion of causality in light of follow-up information and 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 is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated 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 patient dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor and/or CRO 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 the Sponsor and/or CRO within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting

Within 24 hours of identifying an SAE, the Investigator must collect and report the SAE to the designated Pharmacovigilance contact. The SAE reporting must contain all information required for CIOMS reporting. It should contain a place to indicate whether this is an initial or follow-up report.

Minimum information to be documented for the SAE:

- Protocol number
- Name and contact phone number of the Principal Investigator
- Patient number and year of birth
- SAE (preliminary diagnosis and SAE criterion), date of event onset, date of last study drug administration, brief narrative including current status of patient
- Investigator causality assessment MUST be provided
- Concomitant medication information and treatments provided, if applicable
- Relevant laboratory/diagnostic test results and other relevant information

Follow-up information should be provided with the same form with the Follow-up indicated.

After reporting the SAE to Pharmacovigilance, the CRF should be completed for the SAE. This should be updated as the SAE is updated.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

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

Postmenopausal Female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause or has had a hysterectomy and/or oophorectomy (surgical menopause).

A FSH level and LH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (>40 IU/L or mIU/mL) is required.

Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study and undergo pregnancy testing.

Contraception Guidance

All WOBCP and men with partners who are WOBCP must commit to one of the following effective methods of birth control:

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal, injectable) associated with the inhibition of ovulation, initiated at least 30 days prior to Study Day 1.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1.

- Bilateral tubal occlusion/ligation.
- Vasectomized partner, provided the vasectomized partner has received medical confirmation of surgical success, and is the sole heterosexual partner of the WOCBP trial patient.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Practice true abstinence (if acceptable per local requirements): Refraining from heterosexual intercourse. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods, and withdrawal) is not acceptable.

If required by local practices, WOCBP must commit to using 2 methods of contraception.

If during the course of the study a woman becomes surgically sterile or post-menopausal (defined above) and complete documentation is available, contraceptive measures as defined above are no longer required.

It is important to note that the contraception requirements described above are specifically intended to prevent pregnancy during exposure to the investigational therapies. For concomitant immunosuppressive agent(s) (e.g., methotrexate, azathioprine, mycophenolate mofetil, mycophenolic acid, leflunomide, etc.) that have been prescribed per standard of care prior to study entry and are allowed to be continued during the study, contraception should continue while the patient is on the concomitant immunosuppressive agent(s). The duration of contraception after discontinuation of these immunosuppressive agent(s) should be based on the local product labelling. Urine or serum pregnancy testing shall be performed prior to dosing at monthly intervals per the SoA (Section 1.3).

Additional local requirements may apply and should be followed accordingly.

Collection of Pregnancy Information

Male Patients with Partners Who Become Pregnant

The Investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy (until delivery of the fetus or termination of pregnancy). Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Patients Who Become Pregnant

The Investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a patient's pregnancy.

The patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the patient 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. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.

Any female patient who becomes pregnant while participating in the study will discontinue study treatment immediately but will be followed for all subsequent visits.

10.5. Appendix 5: Equivalence of Common Corticosteroid Formulations and Permitted Antimalarials

Medication	**Maximum Daily Dose**
Prednisone	10 mg
Cortisone	50 mg
Hydrocortisone	40 mg
Prednisolone	10 mg
Methylprednisolone	8 mg
Triamcinolone	8 mg
Budesonide	2 mg
Dexamethasone	1.5 mg
Betamethasone	1 to 2 mg

Medication	**Maximum Daily Dose**
Hydroxychloroquine	400 mg
Chloroquine	250 mg twice daily (but not to exceed 5 mg/kg per day)
Quinacrine	100 mg

10.6. Appendix 6: Clinical Endpoints and Disease Activity Instruments

10.6.1. Composite Endpoints Used in this Study

10.6.1.1. SLE Responder Index-4 (SRI-4)

SRI-4 (incorporates data from SLEDAI, BILAG and ssPGA)

At the visit being measured, compared to Screening there must be:

A 4 Point drop in SLEDAI

No 2 new B scores or 1 new A score on BILAG

No increase in Physician's Global Assessment of more than 3 points (10% of the scale)

When used in an endpoint, the requirement for also not stopping study drug or increasing background treatments beyond protocol allowed limits is classically added on which is also the case in this trial.

10.6.1.2. BILAG-based Combined Lupus Assessment (BICLA)

BICLA (incorporates data from BILAG, hSLEDAI, and ssPGA)

At the visit being measured, compared to Screening there must be:

All A scores present at Baseline must drop to B, C or D and B scores to C or D

No worsening in other BILAG organs or the SLEDAI score

No increase in Physician's Global Assessment of 3 or more points (10% of the scale)

No use of off protocol medications or withdrawal from study drug

10.6.2. Clinical Outcome Measures: Glossaries, Scoring Instructions and Forms

Below, we include detailed CRFs, glossaries and scoring algorithms for the main disease scoring instrument to be used in this study. Each of these instruments has been described in Section 8.1.6, in terms of how they are useful, what some of their pitfalls are and how they are integrated into composite endpoints of SRI-4 and BICLA (primary and secondary endpoints) was also reviewed.

10.6.2.1. Form and Glossary for Hybrid SELENA-SLEDAI

10.6.2.1.1. Form

(Circle in SLEDAI score column if descriptor is present at the time of the visit or in the preceding 4 weeks.)

Item no.	SLEDAI score	Descriptor	Definition
1	8	Seizure	Recent onset, exclude metabolic, infectious or drug causes
2	8	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganised, or catatonic behaviour. Exclude uraemia and drug causes
3	8	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes
4	8	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudates or hemorrhages in the choroid, or optic neuritis, scleritis or episcleritis. Exclude hypertension, infection, or drug causes
5	8	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves
6	8	Lupus headache	Severe, persistent headache; may be migrainous, but must be non-responsive to narcotic analgesia. THIS WOULD RARELY BE ATTRIBUTED TO SLE ALMOST NEVER SCORED
7	8	CVA	New onset Cerebrovascular accident(s). Exclude arteriosclerosis
8	8	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages or biopsy or angiogram proof of vasculitis
9	4	Arthritis	> 2 joints with pain and signs of inflammation (i.e. tenderness with swelling or effusion)
10	4	Myositis	Proximal muscle aching/weakness, associated with elevated creatinine phosphokinase (CK)/aldolase, or EMG changes or a biopsy showing myositis
11	4	Urinary casts	Heme-granular or RBC casts
12	4	Hematuria	> 5 RBC/high power field. Exclude stone, infection or other cause
13	4	Proteinuria	> 0.5 gram/24 hours
14	4	Pyuria	> 5 WBC/high power field. Exclude infection
15	2	Rash	Inflammatory type rash

Item no.	SLEDAI score	Descriptor	Definition
16	2	Alopecia	Abnormal, patchy or diffuse loss of hair
17	2	Mucosal ulcers	Oral or nasal ulcerations
18	2	Pleurisy	Pleuritic chest pain or pleural rub or effusion, or pleural thickening (does not require an objective component if medically convincing)
19	2	Pericarditis	Classic pericardial pain and/or rub, effusion or ECG or echocardiogram confirmation (does not require an objective component if medically convincing)
20	2	Low complement	Decrease in CH50, C3 or C4 below lower limit of normal
21	2	Increased DNA binding	Increased DNA binding above normal range for testing laboratory
22	1	Fever	> 38ºC. Exclude infectious cause
23	1	Thrombocytopenia	< 100×10^9 platelets/L, exclude drug causes
24	1	Leukopenia	< 3×10^9 WBC/L, exclude drug causes

Total Score: _____

10.6.2.1.2. Hybrid SELENA-SLEDAI Glossary

GUIDELINES FOR USE OF HYBRID SELENA-SLEDAI MODIFIED FOR ASSESSMENT OVER 28 DAYS TO ASSESS DISEASE ACTIVITY

The hSLEDAI includes the definitions of proteinuria used in the SLEDAI 2K and is otherwise identical to the hSLEDAI.

- The main principle to keep in mind is that this instrument is intended to evaluate current lupus activity and not chronic damage, severity is accounted for in part by the "weightedness" of the scale.
- Points are given exactly as defined.
- A descriptor is either scored the exact points allotted or not scored, i.e. given a zero. Descriptors are scored only if they are present at the time of the physician encounter or in the preceding 28 days. Windows acceptable in a clinical trial are acceptable in scoring the SLEDAI. However, it is never acceptable to fill in gaps which cover activity over 2-3 months or more. The reason for this is that disease activity at the visit might have changed several times in such intervals and the recording of distant activity becomes meaningless.
  Please note that in the original SLEDAI the disease activity being scored was meant to cover only a ten day period, the modification to 28 days is a more useful assessment for use in clinical trials, in order to capture disease activity between monthly visits.

- The descriptor must be documented by the notes written in the physician encounter form and generally applies to the clinical data and not to the laboratory data. The laboratory data is strictly defined as per cutoffs and documentation is provided by the reports from the commercial laboratory.
- Descriptors do not have to be new but can be. They can be ongoing, recurrent, or initial events. Each would be scored the same way. An example would be a malar rash or mucosal ulcer. In these situations a malar rash observed at the initial visit but which remains unchanged for the next six months, irrespective of any treatment, is scored 2 points each time the SLEDAI is completed. Since the nature of lupus is that manifestations are not usually fleeting it would be rare for descriptors to be present 10 days before and not at the time of the encounter. This is discussed in more detail for each descriptor but is especially relevant for the neurologic, pulmonary, and cutaneous manifestations.
- In some descriptors the exclusions written may not be exhaustive. The intent of the SLEDAI is that the descriptor be attributed to SLE. If the physician does not attribute the descriptor to SLE it should not be scored, but full documentation must be provided.

Written in italics is the definition for each descriptor precisely provided in the SLEDAI SCORE

SEIZURE

Definition: Recent onset (last 28 days). Exclude metabolic, infectious or drug cause, or seizure due to past irreversible CNS damage.

This descriptor is scored if the patient has had a witnessed seizure or convincing description (such as tongue biting or incontinence) within 30 days of the current encounter. The patient need not have a positive EEG, CT scan, PET scan, QEEG, or MRI. The CSF may be totally normal.

A seizure is also not counted:

1. If a metabolic cause is determined.
2. In the presence of a proven infectious meningitis, brain abscess, or fungal foci.
3. If there is a history of recent head trauma.
4. In the presence of an offending drug.
5. In the presence of severe hyperthermia or hypothermia.
6. If the patient has stopped taking anticonvulsant medication.
7. If the patient has a documented sub-therapeutic anticonvulsant drug level.

PSYCHOSIS

Definition: Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes.

This descriptor is scored if any of the criteria above are met.

With regard to drug causes the most problematic situation is glucocorticoids. If the treating physician attributes the psychosis to glucocorticoids this descriptor should not be counted.

ORGANIC BRAIN SYNDROME

Definition: Altered mental function with impaired orientation, memory or other intellectual function, with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least two of the following: perceptual disturbance, incoherent speech, insomnia, daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.

a. reduced capacity to focus as exemplified by new inability to perform everyday mathematical computations or disorientation to person, place, time, or purpose
OR inability to carry on a conversation
OR reduction in short term memory

PLUS: Documented abnormality on neuropsychiatric testing

Neuropsychiatric testing may take the form of a "mini-mental-status exam" or a formal neuropsychiatric examination. The important aspect for scoring OBS is that it be reversible. Consideration should be given to the improvement of OBS after institution of glucocorticoids.

This descriptor is not scored in the presence of a metabolic, infectious, or drug cause. If the problem is chronic this descriptor is not scored in SLEDAI but is scored on the damage index.

VISUAL DISTURBANCE

Definition: Retinal and eye changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, optic neuritis, scleritis or episcleritis. Exclude hypertension, infection or drug causes.

This is scored exactly as defined with the understanding that it must be supported by objective evidence.

CRANIAL NERVE DISORDER

Definition: New onset of sensory or motor neuropathy involving cranial nerves. Include vertigo due to lupus.

This is scored exactly as defined and must be supported by objective evidence. However, it should be noted that hydroxychloroquine can affect the eighth cranial nerve.

LUPUS HEADACHE

Definition: Severe persistent headache: may be migrainous, but must be non-responsive to narcotic analgesia.

For this descriptor to be counted, the headache must be present for greater than 24 hours and must not be responsive to narcotic analgesia. Objective documentation need not be present although it is expected that such a complaint, given the severity, would prompt formal testing such as MRI, CT, LP, etc. Furthermore, the headache should be of sufficient severity to warrant

the initiation of glucocorticoids or additional immunosuppressive agents. Scoring of this descriptor means attribution of the headache to CNS lupus.

Most headaches, including most severe and/or migrainous headaches are not attributable to lupus and this descriptor should only be scored very rarely.

CVA

Definition: New onset of cerebrovascular accident (s). Exclude arteriosclerosis or hypertensive causes.

This descriptor is scored if the patient has had a CVA within 28 days of the current encounter. A patient recovering from a CVA that was documented more than 28 days prior to the current encounter is not given points for this descriptor. A patient may have had a previous CVA but to be scored the current CVA must be new.

This descriptor is scored in the presence or absence of anti-phospholipid antibodies, i.e., the precise pathophysiologic mechanism need not be known.

The CVA is scored even in the presence of a normal CT or MRI. A TIA is also scored if the patient gives a convincing history. To exclude atherosclerosis the patient has to have a normal carotid and/or vertebral Doppler and cannot have uncontrolled hypertension.

VASCULITIS

Definition: Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.

To score this descriptor the above definitions must be present. For example, erythematous lesions on the hands or feet which may be characteristically considered "leukocytoclastic vasculitis" but do not fulfill at least one of the above definitions and if not biopsied, are not counted.

Similarly, livedo reticularis is not counted. Healed ulcers with residual scar are not to be counted, but be sure to count these in the damage index.

A lesion consistent with erythema nodosum should be counted regardless of whether it is biopsied or not. Purpura in the presence of a normal platelet count should be counted regardless of whether it has been biopsied or not.

ARTHRITIS

Definition: More than two joints with pain and signs of inflammation, i.e., tenderness, swelling, or effusion.

Arthritis is scored if it is ongoing; it need not be new or recurrent.

Arthritis is scored only if *more than two* joints manifest signs of inflammation. For example if only the right second and left third PIPs are involved or only both wrists, points for this descriptor are not given.

Inflammation is strictly defined in this activity index as the **presence of tenderness** (the patient complains of pain on palpating the joint or upon going through range of motion) **PLUS** any one of the following:

1. swelling
2. effusion
3. warmth
4. erythema, but must exclude overlying cellulitis

The presence of tenderness alone is not sufficient. A patient's complaints of pain in specific joints without objective findings is not sufficient. An exception would be arthritis of the hip in which case pain in the groin on range of motion accompanied by decreased range of motion in the absence of swelling, warmth, or erythema would be counted.

Inflammation of the tendons, ligaments, bursae, and other periarticular structures are not scored. For example, subacromial bursitis and trochanteric bursitis are not scored. If further evaluation reveals osteonecrosis or osteoarthritis, this descriptor is not counted.

MYOSITIS

Definition: Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.

The patient complains of muscle aching and/or weakness in the proximal muscles PLUS one of the following must be present:

1. elevated serum creatine phosphokinase and/or aldolase
2. abnormalities on electromyogram consistent with myositis
3. biopsy-proven myositis

URINARY CASTS

Definition: Heme-granular or red blood cell casts.

This is scored if red blood cell casts are seen, even if it is only one. Pigmented casts are counted but non-pigmented granular casts, hyaline or waxy casts are not counted.

HEMATURIA

Definition: >5 red blood cells/high power field. Exclude stone, infection or other cause.

With regard to this descriptor, every attempt should be made to see patients when they are not menstruating. If this is not possible the urinalysis should be deferred until the next visit.

This descriptor is not scored if there is documented renal calculi or infection. The latter must be confirmed by a positive urinary culture. However, it is acknowledged that associated conditions such as chlamydia or urethral irritation may result in mild hematuria and the physician's best judgment is warranted. **The important point is attribution: there must be other evidence of nephritis and other causes of hematuria must be excluded.**
In the complete absence of proteinuria, attribution of hematuria to active nephritis would be very unlikely unless pathology is limited to the mesangium.

PROTEINURIA

Definition: proteinuria of more than 0.5 g/24 hours.

Must be attributed to active lupus nephritis.

PYURIA

Definition: >5 white blood cells/high power field. Exclude infection.

This descriptor is not scored if there is evidence of vaginal contamination (presence of any squamous epithelial cells) or a documented infection. The latter must be confirmed by a positive urinary culture. However, it is acknowledged that associated conditions such as chlamydia, trichomonas or urethral irritation may result in mild pyuria and the physician's best judgment is warranted. **The important point is attribution; there must be other evidence of nephritis, and other causes of pyuria should be excluded.** In the complete absence of proteinuria, attribution of hematuria to active nephritis would be very unlikely

RASH

Definition: Ongoing inflammatory lupus rash.

A rash is scored if it is ongoing, new or recurrent. Even if it is identical in terms of distribution and character to that observed on the last visit and the intensity is improved, it is counted. Therefore, despite improvement in a rash, if it is still ongoing it represents disease activity. The rash must be attributable to SLE. A description of the rash must appear in the physical exam and should include distribution, characteristics such as macular or papular, and size.

The following should not be scored:

1. Chronic scarred discoid plaques in any location.
2. Transient malar flush, i.e., it is not raised and is evanescent

A common problem one may encounter is the differentiation between scoring a lesion as "rash" and/or "vasculitis". If a lesion meets the descriptive criteria of the latter it should not also be counted as rash, i.e., the score would be 8 points not 10 points. If a separate rash characteristic of SLE is present only then would "rash" also be scored.

ALOPECIA

Definition: Ongoing abnormal, patchy or diffuse loss of hair due to active lupus.

This should be scored if any of the following conditions are present:

1. There is temporal thinning which is newly present for less than six months (if temporal alopecia is present for more than six months with no change it should not be counted)
2. Areas of scalp with total bald spots if present for less than six months (does not need to have accompanying discoid lesion or follicular plugging)
3. The presence of "lupus frizz" i.e., short of strands of unruly hair in the frontal or temporal area

If a patient complains of hair loss and there is nothing apparent on exam this descriptor is not scored.

MUCOSAL ULCERS

Definition: Ongoing oral or nasal ulcerations due to active lupus.

An ulcer is scored if it is ongoing, it need not be new or recurrent. Ulcers can be present in either the nose or oral cavity. Erythema alone without frank ulceration is not sufficient to be scored, even if the erythema is present on the upper palate. Ulcers on the buccal mucosa and tongue are counted.

Mucosal ulcers are not counted as vasculitis.

PLEURISY

Definition: Classic and severe pleuritic chest pain or pleural rub or effusion or new pleural thickening due to lupus.

This descriptor is scored if the patient complains of pleuritic chest pain lasting greater than 12 hours. The pain should be classic, i.e., exacerbated by inspiration, to help distinguish it from musculoskeletal conditions such as costochondritis, which could be confused with pleurisy.

The symptom does not have to be accompanied by any objective findings. The presence of objective findings such as pleural rub or pleural effusions (in the absence of infection, congestive heart failure, malignancy, or nephrosis) is counted, even if not accompanied by symptoms. New pleural thickening should be counted only if other causes as described above are absent.

PERICARDITIS

Definition: Classic and severe pericardial pain or rub or effusion, or electrocardiogram confirmation.

The symptom does not have to be accompanied by objective findings.

LOW COMPLEMENT

Definition: Decrease in CH50, C3 or C4 below the lower limit of normal for testing laboratory.
Exclude a low C4 or CH50 in patients with known inherited deficiency of C4.

INCREASED DNA BINDING

Definition: >25% binding by Farr assay or above normal range for testing laboratory.

FEVER

Definition: >38°C. Exclude infectious cause.

This would be scored if one of the following conditions are present:

1. A documented temperature elevation >100.4°F or >38°C at the time of the visit.
2. A convincing history from the patient that she/he has been febrile within the preceding 10 days prior to the visit without any signs or symptoms suggestive of infection. Febrile is defined as above and not simply that the patient felt feverish. In this case the patient need not be febrile at the time of the visit for a score of 2 to be given.

As stated in the SLEDAI, fever secondary to infection is not to be scored although it is acknowledged that concomitant lupus activity and infection can occur. Fever in the presence of infection should only be scored on the SLEDAI if other evidence of lupus activity is present.

THROMBOCYTOPENIA

Definition: <100,000 platelets/mm^3.

LEUKOPENIA

Definition: <3,000 white blood cells/mm^3. Exclude drug causes.

This is exactly as described, WBC <3,000/mm^3. The presence of an absolute lymphopenia does not count in the SLEDAI. A note of caution, do not confuse this WBC with that used to satisfy the ACR criteria for SLE which is WBC <3,500/mm^3.

With regard to current use of possible offending drugs, the following guidelines are to be considered:

1. The nadir after cyclophosphamide, i.e., low WBC at 10 days after receiving cyclophosphamide in a patient known to have a WBC ≥ 3,000 at the time of receiving cyclophosphamide should not be counted.
2. Do not score leukopenia appearing after initiation of a new medication known to be associated with leukopenia, such as azathioprine or sulfa drugs. If the patient develops a WBC <3000 while taking drugs which may cause leukopenia, score this only if the dosage of medication is unchanged since the last WBC determination.

10.6.2.2. SLEDAI Flare Index (SFI) and Modified SFI

This index can and has been used with any SLEDAI version. As used in the belimumab Phase 3 programs, the same version we are using in this protocol was the SLEDAI version used.

Note: as an experimental endpoint a modified SFI will also be tested which adds a clinician's global distinction between mild and moderate flare and eliminates medication changes as components of a disease flare.

10.6.2.3. SELENA-SLEDAI Physician's Global Assessment (ssPGA)

Visual Analog Scale with anchors

0 1 2 3 *this will be a 100 mm scale*

None Mild Moderate Severe

Mild or Moderate Flare (Is this a mild or is this a moderate flare?)

Change in SELENA-SLEDAI instrument score of 3 points or more (but not to more than 12)

New/worse: Discoid, photosensitive, profundus, bullous lupus,

Nasopharyngeal ulcers

Internal

Pleuritis

Pericarditis

Arthritis

Cutaneous Vasculitis

Fever (SLE)

Increase in prednisone, but not to >0.5 mg/kg/day

Added NSAID or hydroxychloroquine for SLE activity

≥1.0 increase in ssPGA score, but not to more than 2.5

Severe Flare

Change in SELENA-SLEDAI instrument score to greater than 12

New/worse: CNS-SLE

Vasculitis

Nephritis

Myositis

Plt < 60,000

Hemolytic anemia: Hb < 70 g/L or decrease in Hb > 30 g/L

Requiring: double prednisone, or prednisone increase to > 0.5 mg/kg/day, or hospitalization

Increase in prednisone to >0.5 mg/kg/day

New cyclophosphamide, azathioprine, methotrexate for SLE activity

Hospitalization for SLE activity

Increase in Physician's Global Assessment score to >2.5

10.6.2.4. Form, Glossary and Scoring Rules for BILAG

10.6.2.4.1. BILAG Form

Only record items <u>due to SLE Disease Activity</u> & assessment refers to manifestations occurring in the <u>last 4 weeks (compared with the previous 4 weeks)</u>. **♦♦ TO BE USED WITH THE GLOSSARY ♦♦**

Scoring: **ND Not Done**
1 Improving
2 Same
3 Worse
4 New
Yes/No OR Value (where indicated)
❑ indicate if <u>not due to SLE activity</u>
(default is 0 = not present)

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

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

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

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

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

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

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

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

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

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

Internal

10.6.2.4.2. BILAG-2004 Index Glossary

Instructions

- Only record features that are attributable to SLE disease activity and not due to damage, infection, thrombosis (in absence of inflammatory process) or other conditions
- Assessment refers to manifestations occurring in the last 4 weeks compared with the previous 4 weeks
- Activity refers to disease process which is reversible while damage refers to permanent process/scarring (irreversible)
- Damage due to SLE should be considered as a cause of features that are fixed/persistent (SLICC/ACR damage index uses persistence ≥ 6 months to define damage)
- In some manifestations, it may be difficult to differentiate SLE from other conditions as there may not be any specific test and the decision would then lie with the physician's judgement on the balance of probabilities
- Ophthalmic manifestations usually need to be assessed by an ophthalmologist and these items would need to be recorded after receiving the response from the ophthalmologist
- Guidance for scoring:

(4) New

- Manifestations are recorded as new when it is a new episode occurring in the last 4 weeks (compared to the previous 4 weeks) that has not improved and this includes new episodes (recurrence) of old manifestations
- New episode occurring in the last 4 weeks but also satisfying the criteria for improvement (below) would be classified as improving instead of new

(3) Worse

- This refers to manifestations that have deteriorated in the last 4 weeks compared to the previous 4 weeks

(2) Same

- This refers to manifestations that have been present for the last 4 weeks and the previous 4 weeks without significant improvement or deterioration (from the previous 4 weeks)
- This also applies to manifestations that have improved over the last 4 weeks compared to the previous 4 weeks but do not meet the criteria for improvement

(1) Improving

- Definition of improvement:

  (a) The amount of improvement is sufficient for consideration of reduction in therapy and would not justify escalation in therapy

  AND

(b) Improvement must be present currently and for at least 2 weeks out of the last 4 weeks

OR

Manifestation that has completely resolved and remained absent over the whole of last 1 week

(0) Not present

(ND) NOT DONE

- It is important to indicate if a test has not been performed (particularly laboratory investigations) so that this will be recorded as such in the database & not as normal or absent (which is the default)

❑ **Indicate (Tick) if not due to SLE Activity**

- For descriptors that are based on measurements (in renal and haematology systems), it is important to indicate if these are not due to lupus disease activity (for consideration of scoring) as they are usually recorded routinely into a Database

10.6.2.4.3. Change in Severity Category

- There are several items in the index which have been divided into categories of mild and severe (depending on definition). It is essential to record mild and severe items appropriately if the manifestations fulfil both criteria during the last 4 weeks
- If a mild item deteriorated to the extent that it fulfilled the definition of severe category (ie changed into severe category) within the last 4 weeks:

  Severe item scored as new (4)

  AND

  Mild item scored as worsening (3)

- If a severe item improved (fulfilling the improvement criteria) to the extent that it no longer fulfilled the definition of severe category (i.e., changed into mild category) within the last 4 weeks:

  Severe item scored as not present (0) if criteria for severe category has not been met over last 4 weeks **or** as improving (1) if criteria for severe category has been met at some point over last 4 weeks

  AND

  Mild item scored as improving (1) if it is improving over last 4 weeks **or** as the same (2) if it has remained stable over last 4 weeks

Constitutional

1. Pyrexia

   temperature > 37.5˚C documented

2. Unintentional weight loss > 5%

3. Lymphadenopathy

   lymph node more than 1 cm diameter

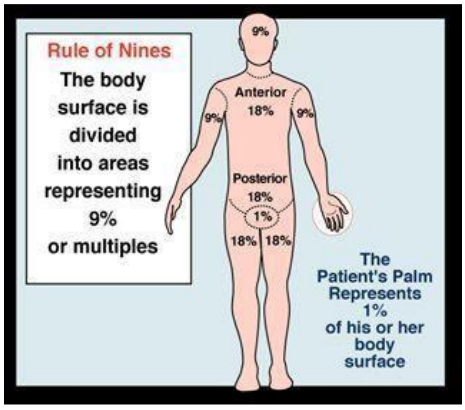
   exclude infection

4. Anorexia

Mucocutaneous

5. Severe eruption

   - 18% body surface area
   - any lupus rash except panniculitis, bullous lesion & angio-oedema
   - body surface area (BSA) is estimated using the rules of nines (used to assess extent of burns) as follows:
     - palm(excluding fingers) = 1% BSA
     - each lower limb = 18% BSA
     - each upper limb = 9% BSA
     - torso (front) = 18% BSA
     - torso (back) = 18% BSA
     - head = 9% BSA
     - genital (male) = 1% BSA



6. Mild eruption

   - ≤ 18% body surface area
   - any lupus rash except panniculitis, bullous lesion & angio-oedema
   - malar rash must have been observed by a physician and has to be present continuously (persistent) for at least 1 week to be considered significant (to be recorded)

7. Severe angio-oedema

   - potentially life-threatening eg: stridor
   - angio-oedema is a variant form of urticaria which affects the subcutaneous, submucosal and deep dermal tissues

8. Mild angio-oedema

   - not life threatening

9. Severe mucosal ulceration

   - disabling (significantly interfering with oral intake), extensive & deep ulceration
   - must have been observed by a physician

10. Mild mucosal ulceration
    - localised &/or non-disabling ulceration
11. Severe panniculitis or bullous lupus
    - any one:
      - > 9% body surface area
      - facial panniculitis
      - panniculitis that is beginning to ulcerate panniculitis that threatens integrity of subcutaneous tissue (beginning to cause surface depression) on > 9% body surface area
    - panniculitis presents as a palpable and tender subcutaneous induration/nodule
    - note that established surface depression and atrophy alone is likely to be due to damage
12. Mild panniculitis or bullous lupus
    - ≤ 9% body surface area does not fulfil any criteria for severe panniculitis (for panniculitis)
13. Major cutaneous vasculitis/thrombosis
    - resulting in extensive gangrene or ulceration or skin infarction
14. Digital infarct or nodular vasculitis
    - localised single or multiple infarct(s) over digit(s) or tender erythematous nodule(s)
15. Severe alopecia
    - clinically detectable (diffuse or patchy) hair loss with scalp inflammation (redness over scalp)
16. Mild alopecia
    - diffuse or patchy hair loss without scalp inflammation (clinically detectable or by history)
17. Peri-ungual erythema or chilblains
    - chilblains are localised inflammatory lesions (may ulcerate) which are precipitated by exposure to cold
18. Splinter haemorrhages

Neuropsychiatric

19. Aseptic meningitis
    - criteria (all):
      - acute/subacute onset
      - headache
      - fever
      - abnormal CSF (raised protein &/or

Internal

  - lymphocyte predominance) but negative
  - cultures
- preferably photophobia, neck stiffness and meningeal irritation should be present as well but are not essential for diagnosis
- exclude CNS/meningeal infection, intracranial haemorrhage

20. Cerebral vasculitis
    - should be present with features of vasculitis in another system
    - supportive imaging &/or biopsy findings
21. Demyelinating syndrome
    - discrete white matter lesion with associated neurological deficit not recorded elsewhere
    - ideally there should have been at least one previously recorded event
    - supportive imaging required
    - exclude multiple sclerosis
22. Myelopathy
    - acute onset of rapidly evolving paraparesis or quadriparesis and/or sensory level
    - exclude intramedullary and extramedullary space occupying lesion
23. Acute confusional state
    - acute disturbance of consciousness or level of arousal with reduced ability to focus, maintain or Shift attention
    - includes hypo- and hyperaroused states and encompasses the spectrum from delirium to coma
24. Psychosis
    - delusion or hallucinations
    - does not occur exclusively during course of a delirium
    - exclude drugs, substance abuse, primary psychotic disorder
25. Acute inflammatory demyelinating polyradiculoneuropathy
    - criteria:
      - progressive polyradiculoneuropathy
      - loss of reflexes
      - symmetrical involvement
      - increased CSF protein without pleocytosis
      - supportive electrophysiology study
26. Mononeuropathy (single/multiplex)
    - supportive electrophysiology study required
27. Cranial neuropathy

- except optic neuropathy which is classified under ophthalmic system

28. Plexopathy
    - disorder of brachial or lumbosacral plexus resulting in neurological deficit not corresponding to territory of single root or nerve
    - supportive electrophysiology study required
29. Polyneuropathy
    - acute symmetrical distal sensory and/or motor deficit
    - supportive electrophysiology study required
30. Seizure disorder
    - independent description of seizure by reliable witness
31. Status epilepticus
    - a seizure or series of seizures lasting ≥ 30 minutes without full recovery to baseline
32. Cerebrovascular disease (not due to vasculitis)
    - any one with supporting imaging:
        - stroke syndrome
        - transient ischaemic attack
        - intracranial haemorrhage
    - exclude hypoglycaemia, cerebral sinus thrombosis, vascular malformation, tumour, abscess
    - cerebral sinus thrombosis not included as definite thrombosis not considered part of lupus activity
33. Cognitive dysfunction
    - significant deficits in any cognitive functions:
        - simple attention (ability to register & maintain information)
        - complex attention memory (ability to register, recall & recognise information eg learning, recall)
        - visual-spatial processing (ability to analyse, synthesise & manipulate visual-spatial information)
        - language (ability to comprehend, repeat & produce oral/written material eg verbal fluency, naming)
        - reasoning/problem solving (ability to reason & abstract)
        - psychomotor speed
        - executive functions (eg planning, organising, sequencing)
    - in absence of disturbance of consciousness or level of arousal
    - sufficiently severe to interfere with daily activities

- neuropsychological testing should be done or corroborating history from third party if possible
- exclude substance abuse

34. Movement disorder
    - exclude drugs
35. Autonomic disorder
    - any one:
        - fall in blood pressure to standing > 30/15 mm Hg (systolic/diastolic)
        - increase in heart rate to standing ≥ 30 bpm
        - loss of heart rate variation with respiration (max – min < 15 bpm, expiration:inspiration ratio < 1.2, Valsalva ratio < 1.4)
        - loss of sweating over body and limbs (anhidrosis) by sweat test
    - exclude drugs and diabetes mellitus
36. Cerebellar ataxia
    - cerebellar ataxia in isolation of other CNS features
    - usually subacute presentation
37. Severe lupus headache (unremitting)
    - disabling headache unresponsive to narcotic analgesia & lasting ≥ 3 days
    - exclude intracranial space occupying lesion and CNS infection
38. Headache from IC hypertension
    - exclude cerebral sinus thrombosis

Musculoskeletal

39. Severe myositis
    - significantly elevated serum muscle enzymes with significant muscle weakness
    - exclude endocrine causes and drug-induced myopathy
    - electromyography and muscle biopsy are used for diagnostic purpose and are not required to determine level of activity
40. Mild myositis
    - significantly elevated serum muscle enzymes with myalgia but without significant muscle weakness
    - asymptomatic elevated serum muscle enzymes not included
    - exclude endocrine causes and drug-induced myopathy
    - electromyography and muscle biopsy are used for diagnostic purpose and are not required to determine level of activity

41. Severe arthritis
    - observed active synovitis ≥ 2 joints with marked loss of functional range of movements and significant impairment of activities of daily living, that has been present on several days (cumulatively) over the last 4 weeks

42. Moderate arthritis or Tendonitis or Tenosynovitis
    - tendonitis/tenosynovitis or active synovitis ≥ 1 joint (observed or through history) with some loss of functional range of movements, that has been present on several days over the last 4 weeks

43. Mild arthritis or Arthralgia or Myalgia
    - inflammatory type of pain (worse in the morning with stiffness, usually improves with activity & not brought on by activity) over joints/muscle
    - inflammatory arthritis which does not fulfil the above criteria for moderate or severe arthritis

Cardiorespiratory

44. Mild myocarditis
    - inflammation of myocardium with raised cardiac enzymes &/or ECG changes and without resulting cardiac failure, arrhythmia or valvular dysfunction

45. Cardiac failure
    - cardiac failure due to myocarditis or non-infective inflammation of endocardium or cardiac valves (endocarditis)
    - cardiac failure due to myocarditis is defined by left ventricular ejection fraction ≤ 40% & pulmonary oedema or peripheral oedema
    - cardiac failure due to acute valvular regurgitation (from endocarditis) can be associated with normal left ventricular ejection fraction
    - diastolic heart failure is not included

46. Arrhythmia
    - arrhythmia (except sinus tachycardia) due to myocarditis or non-infective inflammation of endocardium or cardiac valves (endocarditis)
    - confirmation by electrocardiogram required (history of palpitations alone inadequate)

47. New valvular dysfunction
    - new cardiac valvular dysfunction due to myocarditis or non-infective inflammation of endocardium or cardiac valves (endocarditis)
    - supportive imaging required

48. Pleurisy/Pericarditis
    - convincing history &/or physical findings that you would consider treating

- in absence of cardiac tamponade or pleural effusion with dyspnoea
- do not score if you are unsure whether or not it is pleurisy/pericarditis

49. Cardiac tamponade
    - supportive imaging required
50. Pleural effusion with dyspnoea
    - supportive imaging required
51. Pulmonary haemorrhage/vasculitis
    - inflammation of pulmonary vasculature with haemoptysis &/or dyspnoea &/or pulmonary hypertension
    - supportive imaging &/or histological diagnosis required
52. Interstitial alveolitis/pneumonitis
    - radiological features of alveolar infiltration not due to infection or haemorrhage required for diagnosis
    - corrected gas transfer Kco reduced to < 70% normal or fall of > 20% if previously abnormal
    - on-going activity would be determined by clinical findings and lung function tests, and repeated imaging may be required in those with deterioration (clinically or lung function tests) or failure to respond to therapy
53. Shrinking lung syndrome
    - acute reduction (> 20% if previous measurement available) in lung volumes (to < 70% predicted) in the presence of normal corrected gas transfer (Kco) & dysfunctional diaphragmatic movements
54. Aortitis
    - inflammation of aorta (with or without dissection) with supportive imaging abnormalities
    - accompanied by > 10 mm Hg difference in BP between arms &/or claudication of extremities &/or vascular bruits
    - repeated imaging would be required to determine
    - on-going activity in those with clinical deterioration or failure to respond to therapy
55. Coronary vasculitis
    - inflammation of coronary vessels with radiographic evidence of non-atheromatous narrowing, obstruction or aneurysmal changes

Gastrointestinal

56. Lupus peritonitis
    - serositis presenting as acute abdomen with rebound/guarding

57. Serositis
    - not presenting as acute abdomen
58. Lupus enteritis or colitis
    - vasculitis or inflammation of small or large bowel with supportive imaging &/or biopsy findings
59. Malabsorption
    - diarrhoea with abnormal D- xylose absorption test or increased faecal fat excretion after exclusion of coeliac's disease (poor response to gluten-free diet) and gut vasculitis
60. Protein-losing enteropathy
    - diarrhoea with hypoalbuminaemia or increased faecal excretion of iv radiolabeled albumin after exclusion of gut vasculitis and malabsorption
61. Intestinal pseudo-obstruction
    - subacute intestinal obstruction due to intestinal hypomotility
62. Lupus hepatitis
    - raised transaminases
    - absence of autoantibodies specific to autoimmune hepatitis (eg: anti-smooth muscle, anti-liver cytosol 1) &/or biopsy appearance of chronic active hepatitis
    - hepatitis typically lobular with no piecemeal necrosis
    - exclude drug-induced and viral hepatitis
63. Acute lupus cholecystitis
    - after exclusion of gallstones and infection
64. Acute lupus pancreatitis
    - usually associated multisystem involvement

Ophthalmic

65. Orbital inflammation
    - orbital inflammation with myositis &/or extra-ocular muscle swelling &/or proptosis
    - supportive imaging required
66. Severe keratitis
    - sight threatening
    - includes:
        - corneal melt
        - peripheral ulcerative keratitis

67. Mild keratitis
    - not sight threatening
68. Anterior uveitis
69. Severe posterior uveitis &/or retinal vasculitis
    - sight-threatening &/or retinal vasculitis not due to vaso-occlusive disease
70. Mild posterior uveitis &/or retinal vasculitis
    - not sight-threatening
    - not due to vaso-occlusive disease
71. Episcleritis
72. Severe scleritis
    - necrotising anterior scleritis
    - anterior &/or posterior scleritis requiring systemic steroids/immunosuppression &/or not responding to NSAIDs
73. Mild scleritis
    - anterior &/or posterior scleritis not requiring systemic steroids
    - excludes necrotising anterior scleritis
74. Retinal/choroidal vaso-occlusive disease
    - includes:
        - retinal arterial & venous occlusion
        - serous retinal &/or retinal pigment
        - epithelial detachments secondary to choroidal vasculopathy
75. Isolated cotton-wool spots
    - also known as cytoid bodies
76. Optic neuritis
    - excludes anterior ischaemic optic neuropathy
77. Anterior ischaemic optic neuropathy
    - visual loss with pale swollen optic disc due to occlusion of posterior ciliary arteries

Renal

78. Systolic blood pressure
79. Diastolic blood pressure
80. Accelerated hypertension

- blood pressure rising to > 170/110 mm Hg within 1 month with grade 3 or 4 Keith-Wagener-Barker retinal changes (flame-shaped haemorrhages or cotton-wool spots or papilloedema)

81. Urine dipstick

82. Urine albumin-creatinine ratio

- on freshly voided urine sample
- conversion: 1 mg/mg = 113 mg/mmol it is important to exclude other causes (especially infection) when proteinuria is present

83. Urine protein-creatinine ratio

- on freshly voided urine sample
- conversion: 1 mg/mg = 113 mg/mmol
- it is important to exclude other causes (especially infection) when proteinuria is present

84. 24-hour urine protein

- it is important to exclude other causes (especially infection) when proteinuria is present

85. Nephrotic syndrome

- criteria:
  - heavy proteinuria (≥ 3.5 g/day or protein- creatinine ratio ≥ 350 mg/mmol or albumin-creatinine ratio ≥ 350 mg/mmol)
  - hypo-albuminaemia
  - oedema

86. Plasma/Serum creatinine

- exclude other causes for increase in creatinine (especially drugs)

87. Glomerular Filtration Rate (GFR)

- Modification of Diet in Renal Disease (MDRD) formula:

  GFR = 170 × [serum creatinine (mg/dl)]$^{-0.999}$ × [age]$^{-0.176}$ × [serum urea (mg/dl]$^{-0.17}$ × [serum albumin (g/dl)]$^{0.318}$ × [0.762 if female] × [1.180 if African ancestry]

  units = ml/min per 1.73 m^2

  normal: male = 130 ± 40

  female = 120 ± 40

  conversion:

  serum creatinine - mg/dl = (µmol/l)/88.5

  serum urea - mg/dl = (mmol/l) × 2.8

  serum albumin - g/dl = (g/l)/10

- creatinine clearance not recommended as it is not reliable

- exclude other causes for decrease in GFR (especially drugs)

88. Active urinary sediment

- pyuria (> 5 WCC/hpf or > 10 WCC/mm3 (µl))

  OR

- haematuria (> 5 RBC/hpf or > 10 RBC/mm3 (µl))

  OR

- red cell casts

  OR

- white cell casts
- exclude other causes (especially infection, vaginal bleed, calculi)

89. Histology of active nephritis

- WHO Classification (1995): (any one)
  - Class III – (a) or (b) subtypes
  - Class IV – (a), (b) or (c) subtypes
  - Class V – (a), (b), (c) or (d) subtypes
  - Vasculitis

  OR

- ISN/RPS Classification (2003): (any one)
  - Class III – (A) or (A/C) subtypes
  - Class IV – (A) or (A/C) subtypes
  - Class V
  - Vasculitis
- within last 3 months
- glomerular sclerosis without inflammation not included

Haematological

90. Haemoglobin

- exclude dietary deficiency & GI blood loss

91. White cell count

- exclude drug-induced cause

92. Neutrophil count

- exclude drug-induced cause

93. Lymphocyte count

94. Platelet count

- exclude drug-induced cause

95. TTP

- thrombotic thrombocytopaenic purpura
- clinical syndrome of micro-angiopathic haemolytic anaemia and thrombocytopenia in absence of any other identifiable cause

96. Evidence of active haemolysis

- positive Coomb's test & evidence of haemolysis (raised bilirubin or raised reticulocyte count or reduced haptoglobulins)

97. Isolated positive Coomb's test

Additional Items

These items are required mainly for calculation of GFR

i. Weight

ii. African ancestry

iii. Serum urea

iv. Serum albumin

10.6.2.4.4. BILAG-2004 Index Scoring Rules

Scoring based on the principle of physician's intention to treat.

Category	Definition
A	Severe disease activity requiring any of the following treatment: 1. systemic high dose oral glucocorticoids (equivalent to prednisolone > 20 mg/day) 2. intravenous pulse glucocorticoids (equivalent to pulse methylprednisolone ≥ 500 mg) 3. systemic immunomodulators (include biologicals, immunoglobulins and plasmapheresis) 4. therapeutic high dose anticoagulation in the presence of high dose steroids or immunomodulators eg: warfarin with target INR 3-4
B	Moderate disease activity requiring any of the following treatment: 1. systemic low dose oral glucocorticoids (equivalent to prednisolone ≤ 20 mg/day) 2. intramuscular or intra-articular or soft tissue glucocorticoids injection (equivalent to methylprednisolone < 500mg) 3. topical glucocorticoids 4. topical immunomodulators 5. antimalarials or thalidomide or prasterone or acitretin 6. symptomatic therapy eg: NSAIDs for inflammatory arthritis

Category	Definition
C	Mild disease
D	Inactive disease but previously affected
E	System never involved

Constitutional

Category A

Pyrexia recorded as 2 (same), 3 (worse) or 4 (new) **AND**

Any 2 or more of the following recorded as 2 (same), 3 (worse) or 4 (new):

Weight loss

Lymphadenopathy/splenomegaly

Anorexia

Category B

Pyrexia recorded as 2 (same), 3 (worse) or 4 (new) OR

Any 2 or more of the following recorded as 2 (same), 3 (worse) or 4 (new):

Weight loss

Lymphadenopathy/splenomegaly

Anorexia

BUT do not fulfil criteria for Category A

Category C

Pyrexia recorded as 1 (improving) **OR**

One or more of the following recorded as > 0:

Weight loss

Lymphadenopathy/Splenomegaly

Anorexia

BUT does not fulfil criteria for category A or B

Category D

Previous involvement

Category E

No previous involvement

Mucocutaneous

Category A

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Skin eruption - severe

Angio-oedema - severe

Mucosal ulceration - severe

Panniculitis/Bullous lupus - severe

Major cutaneous vasculitis/thrombosis

Category B

Any Category A features recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Skin eruption - mild

Panniculitis/Bullous lupus - mild

Digital infarcts or nodular vasculitis

Alopecia – severe

Category C

Any Category B features recorded as 1 (improving) **OR**

Any of the following recorded as > 0:

Angio-oedema - mild

Mucosal ulceration - mild

Alopecia - mild

Periungual erythema/chilblains

Splinter haemorrhages

Category D

Previous involvement

Category E

No previous involvement

Neuropsychiatric

Category A

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Aseptic meningitis

Cerebral vasculitis

Demyelinating syndrome

Myelopathy

Acute confusional state

Psychosis

Acute inflammatory demyelinating polyradiculoneuropathy

Mononeuropathy (single/multiplex)

Cranial neuropathy

Plexopathy

Polyneuropathy

Status epilepticus

Cerebellar ataxia

Category B

Any Category A features recorded as 1 (improving) OR Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Seizure disorder

Cerebrovascular disease (not due to vasculitis)

Cognitive dysfunction

Movement disorder

Autonomic disorder

Lupus headache - severe unremitting

Headache due to raised intracranial hypertension

Category C

Any Category B features recorded as 1 (improving)

Category D

Previous involvement

Category E

No previous involvement

Musculoskeletal

Category A

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Severe Myositis

Severe Arthritis

Category B

Any Category A features recorded as 1 (improving) **OR** Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Mild Myositis

Moderate Arthritis/Tendonitis/Tenosynovitis

Category C

Any Category B features recorded as 1 (improving) OR Any of the following recorded as > 0:

Mild Arthritis/Arthralgia/Myalgia

Category D

Previous involvement

Category E

No previous involvement

Cardiorespiratory

Category A

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Myocarditis/Endocarditis + Cardiac failure

Arrhythmia

New valvular dysfunction

Cardiac tamponade

Pleural effusion with dyspnoea

Pulmonary haemorrhage/vasculitis

Interstitial alveolitis/pneumonitis

Shrinking lung syndrome

Aortitis

Coronary vasculitis

Category B

Any Category A features recorded as 1 (improving) **OR** Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Pleurisy/Pericarditis

Myocarditis - mild

Category C

Any Category B features recorded as 1 (improving)

Category D

Previous involvement

Category E

No previous involvement

Gastrointestinal

Category A

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Peritonitis

Lupus enteritis/colitis

Intestinal pseudo-obstruction

Acute lupus cholecystitis

Acute lupus pancreatitis

Category B

Any category a feature recorded as 1 (improving) or any of the following recorded as 2 same), 3 (worse) or 4 (new):

Abdominal serositis and/or ascites

Malabsorption

Protein losing enteropathy

Lupus hepatitis

Category C

Any Category B features recorded as 1 (improving)

Category D

Previous involvement

Category E

No previous involvement

Ophthalmic

Category A

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Orbital inflammation/myositis/proptosis

Keratitis - severe

Posterior uveitis/retinal vasculitis - severe

Scleritis - severe

Retinal/choroidal vaso-occlusive disease

Optic neuritis

Anterior ischaemic optic neuropathy

Category B

Any Category A features recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Keratitis - mild

Anterior uveitis

Posterior uveitis/retinal vasculitis - mild

Scleritis – mild

Category C

Any Category B features recorded as 1 (improving) **OR** Any of the following recorded as > 0:

Episcleritis

Isolated cotton-wool spots (cytoid bodies)

Category D

Previous involvement

Category E

No previous involvement

RENAL

Category A

Two or more of the following providing 1, 4 or 5 is included:

1. Deteriorating proteinuria (severe) defined as

(a) urine dipstick increased by ≥ 2 levels (used only if other methods of urine protein estimation not available); **or**

(b) 24 24-hour urine protein > 1 g that has not decreased (improved) by ≥ 25%; **or**

(c) urine protein-creatinine ratio > 100 mg/mmol not decreased (improved) by ≥ 25%; **or**

(d) urine albumin-creatinine ratio > 100 mg/mmol not decreased (improved) by ≥ 25%

2. Accelerated hypertension

3. Deteriorating renal function (severe) defined as

(a) plasma creatinine > 130 μmol/l and having risen to > 130% of previous value; **or**

(b) GFR < 80 ml/min per 1.73 m2 and having fallen to < 67% of previous value; **or**

(c) GFR < 50 ml/min per 1.73 m2, and last time was > 50 ml/min per 1.73 m2 or not done

4. Active urinary sediment

5. Histological evidence of active nephritis within last 3 months

6. Nephrotic syndrome

Category B

One of the following:

1. One of the Category A features

2. Proteinuria (that has not fulfilled Category A criteria)

(a) urine dipstick which has risen by 1 level to at least 2+ (used only if other methods of urine protein estimation not available); **or**

(b) 24-hour urine protein ≥ 0.5 g that has not decreased (improved) by ≥ 25%; **or**

(c) urine protein-creatinine ratio ≥ 50 mg/mmol not decreased (improved) by ≥ 25%; **or**

(d) urine albumin-creatinine ratio ≥ 50 mg/mmol not decreased (improved) by ≥ 25%

3. Plasma creatinine > 130 μmol/l and having risen to ≥ 115% but ≤ 130% of previous value

Category C

One of the following:

1. Mild/Stable proteinuria defined as

(a) urine dipstick ≥ 1+ but has not fulfilled criteria for Category A & B (used only if other methods of urine protein estimation not available); **or**

(b) 24-hour urine protein > 0.25 g but has not fulfilled criteria for Category A & B; **or**

(c) urine prot-creat ratio > 25 mg/mmol but has not fulfilled criteria for Category A & B; **or**

(d) urine albumin-creatinine ratio > 25 mg/mmol not fulfilled criteria for Category A & B

2. Rising blood pressure (providing the recorded values are > 140/90 mm Hg) which has not fulfilled criteria for Category A & B, defined as

(a) systolic rise of ≥ 30 mm Hg; **and** (b) diastolic rise of ≥ 15mm Hg

Category D

Previous involvement

Category E

No previous involvement

HAEMATOLOGICAL

Category A

TTP recorded as 2 (same), 3 (worse) or 4 (new) **OR** Any of the following:

Haemoglobin < 8 g/dl

White cell count < 1.0×10^9/l

Neutrophil count < 0.5×10^9/l

Platelet count < 25×10^9/l

Category B

TTP recorded as 1 (improving) **OR** Any of the following:

Haemoglobin 8-8.9 g/dl

White cell count 1-1.9 × 10^9/l

Neutrophil count 0.5-0.9 × 10^9/l

Platelet count 25-49 × 10^9/l

Evidence of active haemolysis

Category C

Any of the following:

Haemoglobin 9-10.9 g/dl

White cell count 2-3.9 × 10^9/l

Neutrophil count 1-1.9 × 10^9/l

Lymphocyte count < 1.0 × 10^9/L

Platelet count 50-149 × 10^9/l

Isolated Coombs' test positive

Category D

Previous involvement

Category E

No Previous involvement respectively

10.6.2.5. Clinicians Global Impression of Change (CGIC)

At each visit starting with the Randomization Visit (Baseline, Day 1), the clinician will assess the patient compared to the previous visit, completing the sentence below by selecting the best descriptor from the given choices:

Compared to the last visit the patient's overall lupus disease activity is best described as:

Major or Complete Improvement

Definite Improvement

About the Same or Minor Change

Definite Worsening

Severe Worsening

Note: This scale is a modification of the CGIC defined by Askanase 2019b.

10.6.2.6. Cutaneous Lupus Erythematosus Diseases Area and Severity Index (CLASI) Form with Descriptors

Cutaneous LE Disease Area and Severity Index (CLASI)

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

activity **damage**

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

Mucous membrane

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

Dyspigmentation

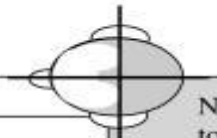
Report duration of dyspigmentation after active lesions have resolved (verbal report by patient – tick appropriate box)

☐ Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains)

☐ Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled)

Alopecia

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



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

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

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

Total Activity Score
(For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrophy, Mucous membrane involvement and Alopecia)

Total Damage Score
(For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation, Scarring/Atrophy/Panniculitis and Scarring of the Scalp)

10.6.2.7. Tender and Swollen Joint Count Form

Assessment: 28 Joint Count Site: 123 Subject: 123456 Visit: Randomization - Date: 21 Oct 2021

Right	Joint	Left
☐ Not Done ☐ Tender ☐ Swollen	Shoulder	☐ Not Done ☐ Tender ☐ Swollen
☐ Not Done ☐ Tender ☐ Swollen	Elbow	☐ Not Done ☐ Tender ☐ Swollen
☐ Not Done ☐ Tender ☐ Swollen	Wrist	☐ Not Done ☐ Tender ☐ Swollen
	(MCP) Metacarpophalangeal	
☐ Not Done ☐ Tender ☐ Swollen	First	☐ Not Done ☐ Tender ☐ Swollen
☐ Not Done ☐ Tender ☐ Swollen	Second	☐ Not Done ☐ Tender ☐ Swollen
☐ Not Done ☐ Tender ☐ Swollen	Third	☐ Not Done ☐ Tender ☐ Swollen
☐ Not Done ☐ Tender ☐ Swollen	Fourth	☐ Not Done ☐ Tender ☐ Swollen
☐ Not Done ☐ Tender ☐ Swollen	Fifth	☐ Not Done ☐ Tender ☐ Swollen
	(PIP) Proximal Interphalangeal	
☐ Not Done ☐ Tender ☐ Swollen	First (IP Thumb)	☐ Not Done ☐ Tender ☐ Swollen
☐ Not Done ☐ Tender ☐ Swollen	Second	☐ Not Done ☐ Tender ☐ Swollen
☐ Not Done ☐ Tender ☐ Swollen	Third	☐ Not Done ☐ Tender ☐ Swollen
☐ Not Done ☐ Tender ☐ Swollen	Fourth	☐ Not Done ☐ Tender ☐ Swollen
☐ Not Done ☐ Tender ☐ Swollen	Fifth	☐ Not Done ☐ Tender ☐ Swollen
☐ Not Done ☐ Tender ☐ Swollen	Knee	☐ Not Done ☐ Tender ☐ Swollen

Right Scores		Total Form Scores		Left Scores	
Tender	0 **14**	Tender	0 **28**	Tender	0 **14**
Swollen	0 **14**	Swollen	0 **28**	Swollen	0 **14**

10.7. Patient-Reported Outcomes

10.7.1. Medical Outcomes Study Questionnaire Short Form 36 Health Survey (SF-36)

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey! For each of the following questions, please circle the number that best describes your answer.

1. In general, would you say your health is:	
Excellent	1
Very good	2
Good	3
Fair	4
Poor	5
2. Compared to one year ago,	
Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same	3
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

(Circle One Number on Each Line)

2. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?	**Yes, Limited a Lot (1)**	**Yes, Limited a Little (2)**	**No, Not Limited at All (3)**
a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing **several** flights of stairs	1	2	3
e. Climbing **one** flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3
g. Walking **more than a mile**	1	2	3
h. Walking **several blocks**	1	2	3
i. Walking **one block**	1	2	3
j. Bathing or dressing yourself	1	2	3

(Circle One Number on Each Line)

3. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical **health**?	**Yes (1)**	**No (2)**
a. Cut down the amount of time you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Were limited in the **kind** of work or other activities	1	2
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

(Circle One Number on Each Line)

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?	**Yes**	**No**
a. Cut down the amount of time you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Didn't do work or other activities as **carefully** as usual	1	2

5. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?	
Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

6. How much bodily pain have you had during the past 4 weeks?	
None	1
Very mild	2
Mild	3
Moderate	4
Severe	5
Very severe	6

7. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	
Not at all	1
A little bit	2
Moderately	3
Quite a bit	4
Extremely	5

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. **(Circle One Number on Each Line)**

8. How much of the time during the past 4 weeks	**All of the Time**	**Most of the Time**	**A Good Bit of the Time**	**Some of the Time**	**A Little of the**	**None of the Time**
a. Did you feel full of pep?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and blue?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

9. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)? (Circle One Number)	
All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

10. How TRUE or FALSE is each of the following statements for you. (Circle One Number on Each Line)	**Definitely True**	**Mostly True**	**Don't Know**	**Mostly False**	**Definitely False**
a. I seem to get sick a little easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

10.7.2. Patients Global Impression Scales (PGIS and PGIC)

Patient's Global Impression of Severity

Since my last visit, my lupus symptoms are best described as:

None
Mild
Moderate
Severe

Patient's Global Impression of Change

Compared to my last visit, my lupus symptoms are best described as:

Major or complete improvement
Definite improvement
About the same
Definite worsening
Severe worsening

10.7.3. FACIT-Fatigue Scale

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

11. Abbreviations

ACR	American College of Rheumatology
ADA	anti-drug antibody(ies)
AE	adverse event
AESI	adverse event of special interest
ALL	all Screened analysis set
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	antinuclear antibody
anti-dsDNA	anti-double-stranded deoxyribonucleic acid
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCR	B cell receptor
BICLA	BILAG-based Combined Lupus Assessment
BILAG	British Isles Lupus Assessment Group
BLyS	B lymphocyte stimulator
BUN	blood urea nitrogen
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CGIC	Clinician's Global Impression of Change
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL	clearance
CLASI	Cutaneous Lupus Erythematous Disease Area and Severity Index
C_{max}	maximum serum concentration

CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CRF	case report form
CRO	contract research organization
C_{trough}	trough concentration
CV%	percent coefficient of variation
DART®	dual affinity re-targeting (protein)
DMARD	disease-modifying antirheumatic drug
ECG	electrocardiogram
ENA	extractable nuclear antigen antibody
EOS	end of study
EULAR	European League Against Rheumatism
FACIT	Functional Assessment of Chronic Illness Therapy
FACS	fluorescence-activated cell sorting
FAS	Full Analysis Set
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
gCV%	geometric percent coefficient of variation
GFR	glomerular filtration rate
GLP	Good Laboratory Practice
GM	geometric mean
GPI	glycoprotein
HAV	hepatitis A virus
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen

HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
HZV	herpes zoster virus
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgA, IgG, IgM	Immunoglobulin A, G, or M
IM	intramuscular
IMG	immunogenicity analysis set
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
IVIG	intravenous immunoglobulin
IVRS	interactive voice response system
IWRS	interactive web response system
LFA	Lupus Foundation of America
LH	luteinizing hormone
LTBI	latent tuberculosis infection
MAD	multiple ascending dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCID	Minimally Clinically Important Difference

MCS	Mental Component Score
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measurements
MRT	mean residence time
mSFI	modified SELENA-SLEDAI Flare Index
NK	natural killer
NSAID	nonsteroidal anti-inflammatory drug
PCS	Physical Component Score
PD	pharmacodynamic(s)
PGIC	Patient's Global Impression of Change
PGIS	Patient's Global Impression of Severity
PK	pharmacokinetic(s)
PP	per-protocol
PRO	patient-reported outcome
PT	prothrombin time
QOL	quality of life
QTcF	QT interval corrected for heart rate using Friderica's cubed root formula
RBC	red blood cell
RDW	RBC distribution width
RNP	Ribonucleoproteins
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation

SELENA	Safety of Estrogens in Lupus Erythematosus National Assessment
SF-36	Short Form 36
SFI	SELENA-SLEDAI Flare Index
SLE	systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
Sm	Smith protein
SoA	Schedule of Activities
SRI-4	Systemic Lupus Erythematosus Responder Index-4
SSA or SSB	Sjögren's A or B
ssPGA	SELENA-SLEDAI Physician's Global Assessment
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TB	tuberculosis
TBNK	T cell, B cell, natural killer cell
TEAE	treatment-emergent adverse event
T_{max}	time to maximum serum concentration
ULN	upper limit of normal
UPCR	urine protein to creatinine ratio
VAS	visual analogue scale
V_d	volume of distribution
V_{ss}	volume of distribution at steady state
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

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