NCT: NCT05087628

STATISTICAL ANALYSIS PLAN

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

Protocol Number:	PRV-3279-2a
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Statistical Project Leader:	[redacted] Sanofi

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List of Abbreviations

ADA	Anti-drug antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALL	All Screened Population
BICLA	BILAG-based Combined Lupus Assessment
BILAG	British Isles Lupus Assessment Group
CAC	Central Adjudication Committee
CFR Part 11	Code of Federal Regulations Part 11
CGIC	Clinician's Global Impression of Change
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CSR	Clinical Study Report
dsDNA	double stranded deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of Study
EULAR	European League Against Rheumatism
FAS	Full Analysis Set
GM	Geometric Mean
IDMC	Independent Data Monitoring Committee
IM	Intramuscular
IMG	Immunogenicity
IRR	Infusion-Related Reaction
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LFA	Lupus Foundation of America
MedDRA	Medical Dictionary for Regulatory Activities
MCS	Mental Component Score of the SF-36
MRM	Model for Repeated Measures
NSAID	Non-steroidal anti-inflammatory drug
PCI	Potentially Clinically Important
PCS	Physical Component Score of the SF-36
PD	Pharmacodynamics
PGIC	Patient's Global Impression of Change
PGIS	Patient's Global Impression of Severity
PK	Pharmacokinetics
PP	Per-Protocol
PPD	Pharmaceutical Product Development, Inc.
PT	Preferred Term
QTcF	Corrected QT Interval (Fridericia's Correction)
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation

SELENA-SLEDAI	Safety of Estrogens in Lupus Erythematosus National Assessment – System Lupus Erythematosus Disease Activity Index
SF-36	Short Form 36 Health Survey
SEM	Standard Error of the Mean
SLE	Systemic Lupus Erythematosus
SoA	Schedule of Activities
SOC	System Organ Class
SRI-4	SLE Responder Index-4
ssPGA	SELENA-SLEDAI Physician's Global Assessment
TBNK	T cell, B cell, natural killer cell
TEAE	Treatment-emergent Adverse Event

1 INTRODUCTION

This is a statistical analysis plan (SAP) for study PRV-3279-2a (PREVAIL-2). This SAP describes the statistical analyses which will be performed and presented in the Clinical Study Report (CSR).

This SAP is written based on the following study documents:

- Protocol v2.0 (16 December 2022)
- Protocol v2.1 (China) 16DEC2022
- Electronic Case Report Forms (eCRF) v5.0 (24 April 2023)

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Endpoint

Objective	Endpoint
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 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

[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)

2.2 Secondary Objectives and Endpoints

Objectives	Endpoints
Efficacy	
To evaluate whether PRV-3279 prolongs the duration of disease amelioration induced by corticosteroids before Day 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
To determine whether PRV-3279 allows patients to achieve and sustain European League Against Rheumatism (EULAR) – recommended treatment goal of low disease	Proportion of patients who meet either of the following criteria at Week 24: • hSLEDAI score <3 **OR** • All BILAG scores are C or less
To evaluate the effect of PRV-3279 on patient-reported physical functioning	Change from Screening to Week 24 in the Physical Component Score (PCS) in the Short Form 36 Health Survey (SF-36)
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)	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
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	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 and Anti-drug antibody (ADA) titers.

2.3 Exploratory Objectives and Endpoints

Objectives	Endpoints
[redacted]	[redacted]

For China, no exploratory objectives were defined.

3 STUDY DESIGN

This is a randomized, double-blind, placebo-controlled study in adult patients with active systemic lupus erythematosus (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 end of study (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.

Patients in screening will be evaluated by a Central Adjudication Committee (CAC) for determination of initial eligibility to be randomized. A patient must have CAC approval to randomize AND also have eligibility confirmed at the Randomization visit by the Investigator in terms of patient improvement over the Screening period 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).

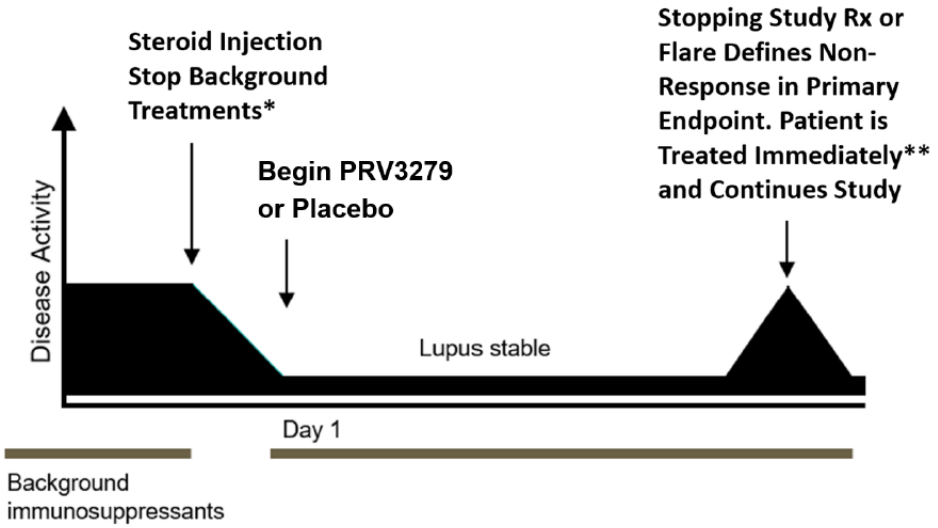
The assessments by hSLEDAI and BILAG Index at the Randomization visit will be scored by a simple clinical comparison of SLE disease activity at Week 0 (Day 1, Randomization Visit) and the Screening visit.

[redacted].

If a lupus flare occurs (as defined by the primary endpoint), 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) in the study protocol. The CAC will, independently of the Investigator, make a determination as to whether suspected flares meet the definition of lupus flare.

The study design is described in Figure 1.

Figure 1 - PRV-3279-2a Schematic



*All background SLE treatments are stopped or tapered after the Screening visit (before 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.

4 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 of 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 group and control group, respectively (Merrill 2018). [redacted].

5 ANALYSIS POPULATIONS

The analysis sets are defined as follows:

Table 1 - Analysis Sets

Analysis Set	Definition
All Screened (ALL) analysis set	All screened patients
Full analysis set (FAS)	All randomized patients who received at least one dose of study treatment. Patients will be analyzed according to the randomized treatment. The FAS will be used for efficacy analysis.
Per-Protocol (PP) analysis set	All patients in the FAS 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 the unblinding of the study. Criteria may include: • Randomization mis-stratification • Randomization in error • Not being 100% treatment compliant (see Section 8.4) • Receipt of prohibited SLE medication or increased dose of allowable SLE medication (in the absence of lupus flare) The analysis of the primary efficacy endpoint will also be performed on the PP set.
Safety analysis set (SAF)	All patients who take at least one dose of the study drug post-randomization. Patients will be analyzed according to the treatment actually received. The SAF analysis set will be used for all safety analyses.
Pharmacokinetic (PK) analysis set	All randomized patients who received at least one dose of the study drug and have at least one post-dose evaluable PK assessment.
Immunogenicity (IMG) analysis set	All randomized patients who received at least one dose of the study drug and have at least one post-dose evaluable IMG assessment.
Pharmacodynamic (PD) analysis set	All randomized patients who received at least one dose of the study drug and have at least one post-dose evaluable PD assessment.

For China no PD analysis set was defined.

6 GENERAL STATISTICAL CONSIDERATIONS

6.1 Analysis Quality Assurance

PPD, a Contract Research Organization part of Thermo Fisher Scientific, will conduct the statistical analyses for this study. All tables, figures, and data listings to be included in the CSR will be independently checked for consistency, integrity, and in accordance with PPD's standard operating procedures.

6.2 General Presentation Considerations

Summary tables will be presented by treatment group (PRV-3279 or Placebo), unless otherwise specified. A total column may be included if appropriate. Data listings will include treatment group, patient identification number, age at screening, sex, and race at a minimum.

For continuous variables, the following descriptive statistics will be provided in summaries, unless otherwise specified: number of non-missing observations (n), mean, standard deviation (SD), median, minimum, and maximum.

For categorical variables, number of non-missing observations and percentages will be displayed. Denominators for percentages are the number of patients in the relevant analysis set and treatment group, unless otherwise specified.

All statistical inferences will be based on 2-sided tests with an α-level of 0.05 unless otherwise specified. In general, p-values will be presented to three decimal places. A p-value greater than 0.999 will be presented as ">0.999"; similarly, a p-value less than 0.001 will be presented as "<0.001".

The observation period will be divided into 3 segments:

- The **pre-treatment** period is defined as the period up to first IMP administration.
- The **TE period** is defined as the period from the first IMP administration to the last IMP administration + 56 days (ie, to the end of 8 weeks safety follow-up period).
- The **post-treatment period** defined as the period from the end of the TE period.

6.3 Definition of Baseline

Unless otherwise specified, a baseline value will be the last non-missing value prior to the first dose of study drug. If an assessment occurs on the same day as the first dose of study drug, and the timing of the assessment cannot be determined relative to dosing, it will be assumed the assessment occurred prior to the dosing.

6.4 Analysis Visit Windows

By-visit table summaries will not have visit windows applied. Data summaries will be displayed by nominal visit where applicable. Any unscheduled results will be included in data listings.

6.5 Handling of Missing Values

Missing values will not be imputed in summaries or data listings, unless otherwise specified.

6.6 Handling of Partial Dates

In general, partial or missing dates will not be imputed.

For medications, if it cannot be determined via partial dates that a medication is strictly a prior medication or a concomitant medication, the medication will be considered as a concomitant medication.

For time since lupus diagnosis (in days) the following approach will be used for handling partial dates. If day is missing, but month and year are present, the date is set to first day of the month. If day and month is missing, but year is present, the date is set to first of January.

6.7 Software

All outputs will be produced using SAS® version 9.4 or later in a secure and validated CFR Part 11 compliant environment.

6.8 Interim Analysis

No interim analyses of efficacy will be conducted for this study. Safety will be regularly assessed by an Independent Data Monitoring Committee (IDMC). Details are provided in a separate IDMC charter.

7 STUDY ASSESSMENTS

7.1 Efficacy Assessments

Efficacy will be assessed through several instruments completed by the investigator as well as patient-reported outcomes. Refer to the study protocol for more details.

7.1.1 Investigator Assessments

Hybrid Systemic Lupus Erythematosus Disease Activity Index (hSLEDAI)

The hSLEDAI will be completed at all planned study visits (and flare assessment visits) and is scored for disease activity. Scores are calculated as the sum of the scores from the 24 individual items on the assessment. Higher scores are associated with greater disease activity.

An increase in hSLEDAI score from baseline is a component of the lupus flare definition as part of the primary efficacy endpoint. A decrease in hSLEDAI score is a component of the secondary efficacy endpoint for SRI-4 criteria at 24 weeks, and reaching a threshold of <3 is a component of the secondary efficacy endpoint for EULAR League at 24 weeks.

SELENA-SLEDAI Physicians Global Assessment (ssPGA)

The ssPGA will be completed at all planned study visits (and flare assessment visits) and contains a visual analog scale component denoting None, Mild, Moderate, or Severe disease, with scores between 0 and 1, between 1 and 2, and between 2 and 3 respectively.

Increases in the ssPGA score are part of the secondary efficacy endpoints for SRI-4 criteria and BICLA criteria at 24 weeks.

SELENA-SLEDAI Flare Index (SFI)

The SFI will be completed at all planned study visits (and flare assessment visits) and capture information pertaining to changes in hSLEDAI scoring, medication changes, and assessment of new or worsening descriptive features of active SLE. The SFI may be evaluated in an exploratory efficacy analysis.

Modified SELENA-SLEDAI Flare Index (mSFI)

The mSFI will be completed at all planned study visits (and flare assessment visits) and follows the format of the SFI except for (1) a removal of medication rules and (2) collection of investigator opinion distinguishing between a mild and moderate flare.

The mSFI may be evaluated in an exploratory efficacy analysis.

British Isles Lupus Assessment Group (BILAG) Index

The BILAG will be completed at all planned study visits (and flare assessment visits) and consists of 97 descriptors for signs and symptoms of lupus divided into 9 organ systems. This instrument scores disease activity within the last month, and each of the organ systems receives a score 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).

The BILAG score is a component of both the definition of lupus flare for the primary efficacy endpoint and the EULAR-League, SRI-4, and BICLA criteria at Week 24 secondary efficacy endpoints.

Clinician's Global Impression of Change (CGIC)

The CGIC will be completed at all planned visits (and flare assessment visits) except the Screening visit. It assesses a patient's change in overall lupus disease activity since the previous visit as "Major or Complete Improvement", "Definite Improvement", "About the Same or Minor Change", "Definite Worsening", or "Severe Worsening".

The CGIC is a component of the definition of lupus flare for the primary efficacy endpoint.

Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)

The CLASI will be completed at all planned study visits (and flare assessment visits). This instrument is based on objective findings in the mucocutaneous system on the day of the visit. The CLASI produces both a Total Activity Score (sum of left side items) as well as a Total Damage Score (sum of right side items), with higher scores denoting worse disease severity.

The CLASI may be evaluated in an exploratory efficacy analysis.

Tender and Swollen Joint Count

The 28-joint count will be completed at all planned study visits (and flare assessment visits). This instrument provides an assessment of whether each joint is tender (yes/no) or swollen (yes/no). The total number of right side, left side, and overall joints which are tender or swollen produce the scores for this instrument.

The Tender and Swollen Joint Count may be evaluated in an exploratory efficacy analysis.

7.1.2 Patient-Reported Outcomes

Short Form 36 Health Survey (SF-36)

The SF-36 will be completed at all planned study visits (and flare assessment visits). This instrument provides an assessment of quality of life over eight domains. Scoring ranges from 0 to 100 with higher scores designating better health. Two summary scores, the PCS and the Mental Component Score (MCS) are produced.

Changes in the PCS over time will be evaluated as part of a secondary efficacy endpoint.

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

The FACIT-F will be completed at all planned study visits (and flare assessment visits). This instrument evaluates both physical and mental fatigue. The assessment contains 13 items

scored on a four-point scale (0 – Not at all, 1 – A little bit, 2 – Somewhat, 3 – Quite a bit, 4 – Very much), and the range of scores is 0-52 (with lower FACIT Fatigue subscale scores indicating more fatigue). Rules for calculating the FACIT-F subscale score are in Appendix 13.2.

FACIT-F scores may be evaluated in an exploratory efficacy analysis.

Patient Global Impression of Severity (PGIS)

The PGIS will be completed at all planned study visits (and flare assessment visits). The version at Screening will evaluate the patient's perception of lupus symptoms over the prior month, and subsequent versions will evaluate since the previous visit. The PGIS is a single item with four possible responses: "None", "Mild", "Moderate", "Severe" with respect to the patient's description of their lupus symptoms.

The PGIS may be evaluated in an exploratory efficacy analysis.

Patient Global Impression of Change (PGIC)

The PGIC will be completed at all planned study visits (and flare assessment visits). The version at Screening will evaluate the patient's perception of the change in their lupus symptoms over the prior month, and subsequent versions will evaluate since the previous visit. The PGIC is a single item with five possible responses: "Major or complete improvement", "Definite improvement", "About the same", "Definite worsening", "Severe worsening" with respect to the patient's description of the change in their lupus symptoms.

The PGIC may be evaluated in an exploratory efficacy analysis.

7.2 Safety Assessments

7.2.1 Adverse Events

Adverse events will continually be recorded in the eCRF from Screening through the end of study. Treatment-emergent adverse events (TEAE) and Adverse Events of Special Interest (AESI) will be summarized.

7.2.2 Clinical Laboratory Measurements

Clinical laboratory measurements (Hematology, Chemistry, Coagulation, and Urinalysis) will be collected at all study visits. Values and changes over time, potentially clinically important criteria, and liver function tests will be evaluated.

7.2.3 Physical Examination

A complete physical examination will be conducted at Screening, followed by brief physical examinations at all subsequent visits. Any abnormal clinically significant findings will be summarized.

7.2.4 Vital Signs

Vital sign measurements will be assessed at all study visits. On dosing days, vital sign assessment will occur prior to dosing and also within 30 minutes after the end of infusion. Values and changes over time from Baseline will be evaluated.

Weight decreases of >=10% from Baseline will also be evaluated.

7.2.5 12-lead Electrocardiogram

A 12-lead Electrocardiogram (ECG) will be performed at all study visits except Flare Assessment visits. Values of the ECG will be evaluated, and any abnormal clinically significant findings will be noted.

7.3 Other Assessments

7.3.1 Pharmacokinetics

Pharmacokinetic (PK) samples will be collected at all study visits except Screening. On dosing days, samples will be collected within 30 minutes pre-dose and within 5 minutes after the end of infusion. For patients who consent to additional PK sampling, additional post-infusion samples will be collected on Day 1 and Day [redacted].

Descriptive summaries of PK concentrations will be produced, and noncompartmental analysis findings will be produced for patients who consent to additional PK sampling.

7.3.2 SLE Serology and Disease Activity Markers

Samples for SLE serology will be collected at Screening, Week 12, Week 24, the Week 28 (EOS) visit, and the early termination visit, if applicable. 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.

Samples for SLE disease activity markers will be collected at all study visits and will include tests for serum anti-dsDNA antibodies, complement components C3 and C4, and a total serum immunoglobulin profile.

7.3.3 TBNK Panel

Samples for a TBNK panel will be collected at all study visits.

7.3.4 [redacted]

[redacted]

7.3.5 Anti-Drug Antibodies

Samples for anti-drug antibodies (ADA) will be collected at all study visits except Screening for the purpose of evaluating immunogenicity.

7.3.6 Pharmacodynamic Markers

[redacted]

7.3.7 Receptor Occupancy

Samples for receptor occupancy will be collected at all study visits except Screening in patients who consent to receptor occupancy sampling. Additional samples will be collected on Day 1 and Day [redacted].

8 STUDY PATIENTS

8.1 Disposition

The following patient disposition information will be summarized by treatment group:

- Randomized and not exposed
- Randomized and exposed
    - Still on study treatment or missing end of treatment page
    - Completed the study treatment period
    - Did not complete the study treatment period
    - Reason for study treatment discontinuation
- Completed the study period
- Did not complete study period, including reason
- Status at last contact

The number and percentage of patients screened and screen failures will be presented overall.

Disposition of screened participants will be summarized by country and site, including the number and percentage of patients screened, screen failures, patients randomized and exposed, patients with permanent treatment discontinuation and premature end of study.

The number and percentage of patients in each analysis set will also be presented by treatment group and overall.

Disposition will be summarized on the ALL analysis set.

Information on participant randomization & participants exposed but not considered as randomized will be listed by subject on the ALL analysis set. Information on cases where the code was broken at local level will be listed by subject on the FAS.

8.2 Protocol Deviations

Protocol deviations will be identified on an ongoing basis by the clinical study team.

Assessment of protocol deviations will be performed periodically by the study team during the study and the list of patients with protocol deviations, including the classification of the protocol deviations (major vs minor), will be finalized prior to database lock and study unblinding.

The number and percentage of patients in the FAS with at least one critical or major protocol deviation will be summarized by deviation type and by treatment group.

Information on patients with at least one critical or major deviation will be listed on the FAS.

8.3 Demographics, Baseline Characteristics, prior and concomitant medications

The following demographics and baseline characteristics, medical and surgical history and disease characteristics at baseline will be summarized for the FAS by treatment group and overall.

Demographic and baseline characteristics

- Age at Screening (Years)
- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Decline to Answer
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Decline to Answer, Unknown)
- Region (North America, Asia)
- Method of Contraception (combined hormonal contraception, progestogen only contraception, bilateral tubal occlusion/ligation, vasectomy, vasectomized partner, intrauterine device, intrauterine hormone releasing system, practice true abstinence, other)
- Fertility Status (Female of Reproductive Potential, Sexually Active Male with Female Partner of Reproductive Potential, Sexually Active Male with Female Partner not of Reproductive Potential, Surgically Sterile, Post-Menopausal, Permanent Infertility, Other)
- Height at Baseline (cm)
- Weight at Baseline (kg)

Disease characteristics at baseline

- Time since Lupus Diagnosis to Randomization (Years), calculated as (Date of Randomization – Date of Lupus Diagnosis)/365.25
- Anti-dsDNA antibodies (Presence, Absence) per IWRS
- [redacted]
- IM Corticosteroids type during Screening (methylprednisolone acetate, methylprednisolone sodium succinate, other)
- Total dose of IM Corticosteroids during Screening (mg)

Any technical details related to computation, dates, and imputations for missing dates are described in Section 6.5 and Section 6.6.

Medical or surgical history

Medical (or surgical) history includes all the relevant medical (or surgical) history during the lifetime of the participant. Medical and surgical history will be coded to a PT, HLT, HLGT, and associated primary SOC using the MedDRA version in effect at Sanofi at the time of database lock.

- **Lupus medical History** will be summarized separately:

A summary table will be created on the FAS to describe lupus history based on the historical BILAG by treatment group and overall. The BILAG categories (e.g. Constitutional, Mucocutaneous, etc.) and individual manifestations within BILAG category will be presented along with the number and percentage of patients with at least one manifestation.

Prior or concomitant medications

- **Prior SLE Medications**

Prior SLE treatments are those reported in the Lupus Diagnosis and Prior Treatments eCRF and which start and stop prior to the first dose of study treatment. Prior SLE treatments that are coded with the WHODrug Dictionary (March 2022 or the latest available dictionary at the time of database lock) will be summarized by Anatomical Therapeutic Chemical (ATC) level1 and ATC level 2 by treatment group and overall, on the FAS.

- **Concomitant SLE Medications**

Concomitant SLE treatments are those entered in the Current SLE treatment eCRF and either begin prior to the first dose of study treatment and continue into the treatment period or begin on or after the first dose of study treatment. Concomitant SLE treatments that are coded with the WHODrug Dictionary will be summarized by ATC level 1 and ATC level 2 by treatment group and overall on the FAS.

Taking prohibited SLE treatments, starting new concomitant SLE treatments, or increasing the dose of allowed concomitant SLE treatments will result in the patient being considered a non-responder in the primary efficacy analysis.

- **Non-SLE Medications**

Prior and Concomitant non-SLE medications will be summarized separately by ATC level 1 and ATC level 2 and preferred name, by treatment group and overall, on the FAS. Prior non-SLE medications are those that start and stop by the time of the first dose of study treatment. Concomitant non-SLE medications are those that begin prior to the first dose of study treatment and continue into the treatment period or those that begin on or after the first dose of study treatment.

8.4 Treatment Compliance

The administration of study treatment occurs in the clinic on Day 1 and every 4 weeks thereafter through Week 20 (6 doses in total), and detailed information is captured in the Study Drug Administration eCRF.

A given administration will be considered noncompliant if the participant did not receive the full volume of infusion and number of administration days as required by the protocol.
No imputation will be made for participants with missing or incomplete data.

Percentage of treatment compliance for a participant will be defined as the number of administrations that the participant was compliant divided by the total number of administrations that the participant was planned to take from the first administration of IMP up to the actual last administration of IMP. If the patient discontinued early, the denominator is counted as the total number of administrations planned before discontinuation. The same approach is used for patients with treatment failure.

Please see the Section 10.1 for a description of summaries of these data.

9 EFFICACY EVALUATION

All efficacy analyses will be performed on the FAS and the PP analysis set.

9.1 Primary Efficacy Endpoint

The primary endpoint is the proportion of patients who maintain improvement in SLE disease activity (i.e. "responder") from Baseline to Week 24, defined as

- Having no lupus flare during this period (based on CAC adjudication) **AND**
- Not missing 2 consecutive doses or 3 or more total doses of study drug for any reason **AND**
- Not taking a new SLE medication or increasing the dose of an allowed SLE medication (with the exception of NSAIDs)

For this analysis, a new SLE medication is one prescribed for SLE treatment and which is not taken at baseline and is prescribed during the period from Baseline to Week 24. An increase in dose of an allowed SLE medication is considered to be any clinically significant increase in dose prescribed by a physician and which occurs during the period from Baseline to Week 24.

Patients who do not maintain improvement from Baseline to Week 24 will be considered non-responders. Patients who withdraw from the study prior to Week 24 for any reason are included in the primary analysis and considered non-responders in statistical testing.

9.1.1 Statistical Hypotheses

The null hypothesis is that the proportion of responders in the PRV-3279 group is the same as in the placebo group. The alternative hypothesis is that the proportion of responders is different between the PRV-3279 group and the placebo group.

9.1.2 Statistical Methods

The difference in the proportion of responders between the PRV-3279 and the placebo groups will be tested using the Cochran-Mantel-Haenszel (CMH) test accounting for the randomization stratification factors anti-dsDNA antibodies: Presence vs Absence and [redacted]: High vs Low. 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 estimate of the CMH weighted risk difference and corresponding Wald 80% CI and Wald test using Sato variance will be provided. All data collected after study intervention discontinuation will be used in the analysis. Participants who discontinue the study without having an event of flare will be considered as non-responder.

The number and percentage of responders, non-responders, and those with missing status (i.e. unable to determine responder status due to lack of data) in each treatment group, the associated 80% confidence intervals (CI) in each group, the difference in proportion of responders, and the associated 80% confidence interval for the difference in proportion will be

provided. The p-value from the CMH method will be provided based on a test where patients with missing status are treated as non-responders.

The primary efficacy analysis will be repeated for the PP set.

9.1.3 Sensitivity Analysis for the Primary Efficacy Analysis

No sensitivity analysis will be performed for the primary efficacy analysis.

9.2 Secondary Efficacy Analysis

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

9.2.1 Time to Treatment Failure

A patient will be considered to have failed treatment if at least one of the following occurs on or after the first dose of study treatment:

- Occurrence of a lupus flare (as defined in the primary efficacy endpoint based on CAC adjudication) **OR**
- Missing 2 consecutive doses or 3 or more total doses of study drug for any reason **OR**
- Starting a new SLE medication or increasing the dose of an allowed SLE medication (with the exception of NSAIDs) **OR**
- Patient withdraws from the study before the Week 24 visit

The definition of starting a new SLE medication or increasing the dose of an allowed SLE medication (with the exception of NSAIDs) will follow the same definition used in the analysis of the primary efficacy endpoint.

Patients who are not considered to have failed treatment will be censored at the Date of Study Completion. The time to treatment failure in weeks will be calculated as shown in Table 2:

Table 2 - Time to Treatment Failure

Event Type	Time to Treatment Failure calculation
Treatment Failure	(Date of Treatment Failure – Date of Randomization + 1)/28 where Date of Treatment Failure is the earliest of the following: • Date patient first started experiencing symptoms of a lupus flare (adjudicated as a lupus flare per CAC), as captured on the Flare Assessment eCRF • Actual Date of the visit where the 2nd consecutive study treatment or 3rd dose of study treatment is missed if the visit occurred; if actual visit date is not available, the planned visit date should be calculated based on the last available visit date and a 4-week increment between visits

Event Type	Time to Treatment Failure calculation
	• Earliest post-randomization date of a new SLE treatment or increase in dose of an allowed SLE medication (with the exception of NSAIDs) • Date of study discontinuation
Censoring	(Date of Study Completion – Date of Randomization + 1)/28

The time to treatment failure (month) will be summarized by treatment group using Kaplan-Meier methods. The 25th, 50th, and 75th percentiles of time to treatment failure and associated 95% CI, number of events, and the number censored will be displayed for each treatment group. The percentages of subjects free from treatment failure at 1, 2, 3, 4, 5, and 6 months will be provided along with 95% CI. A stratified log-rank test will be used to test for differences between treatment groups.

Kaplan-Meier plots of the time to treatment failure will also be provided.

9.2.2 EULAR-recommended Goal of Low Disease at Week 24

The proportion of patients who meet either of the following criteria at Week 24 (i.e., responder) will be compared between the PRV-3279 and Placebo groups:

- Hybrid SELENA-SLEDAI (hSLEDAI) score <3 **OR**
- All BILAG scores are C or D or E

Any patients who do not have available data at Week 24 to be able to assess this endpoint will be considered non-responders for statistical testing.

The proportion of responders will be compared using a CMH test (or Fisher's Exact test as appropriate) in the same manner as the primary efficacy endpoint.

9.2.3 Patient-Reported Physical Functioning

The SF-36 PCS will be calculated by the QualityMetric Health Outcomes^{TM} Scoring Software (3), for each patient at each time point. Details about the scoring method are available in Section 13.3.

The change in PC score from Screening to Week 24 will be compared between the PRV-3279 and Placebo groups using a linear mixed effect modelling for Repeated Measurements (MMRM) assuming data missing at random (MAR). The model will include treatment, visit randomization stratification factors, and the Screening score as fixed effects, treatment by visit as interaction term, and subject as random effect. A model considering an unstructured covariance matrix will be first examined. If the model cannot be fit with the unstructured covariance matrix, a AR(1) covariance matrix will be considered. If the model still cannot be fit, a compound symmetry covariance structure will be considered.

The estimated treatment change in PCS score at Week 24 (and its 80% CI) in each treatment group as well as the difference (and its 80% CI) between the PRV-3279 and Placebo groups will

be provided in a summary table. Additional summaries of estimated treatment changes (and their 80% CI) and the differences at other study visits will also be provided.

9.2.4 SRI-4 at Week 24

The proportion of patients who achieve SRI-4 at Week 24 (i.e., responder) will be compared between the PRV-3279 and Placebo groups. The SRI-4 criteria are defined as follows:

- hSLEDAI score decrease of ≥4 points from Screening **AND**
- no new organs with a BILAG A (severe) score as compared to Screening **AND**
- no more than 1 new organ with a BILAG B (moderate) score as compared to Screening **AND**
- no ssPGA score increase of >0.3 points from Screening

Any patient in the FAS who does not meet the criteria for a responder will be considered a non-responder in the statistical testing.

The proportion of responders will be compared using a CMH method in the same manner as the primary efficacy endpoint.

9.2.5 BICLA criteria at Week 24

The proportion of patients who meet the BICLA criteria at Week 24 (i.e., responder) will be compared between the PRV-3279 and Placebo groups. The BICLA criteria are defined as follows:

- Reduction by ≥1 grade in all organs with BILAG A or B scores from Screening **AND**
- No worsening of SLEDAI or other BILAG organs from Screening **AND**
- No ssPGA score increase of >0.3 points from Screening

Any patient in the FAS who does not meet the criteria for a responder will be considered a non-responder in the statistical testing.

The proportion of responders will be compared using a CMH method in the same manner as the primary efficacy endpoint.

9.2.6 Sensitivity Analysis for Time to Treatment Failure Endpoint

No sensitivity analysis for the time to treatment failure endpoint will be performed.

9.3 Exploratory Efficacy Analysis

The following exploratory efficacy analyses may be conducted as appropriate:

- [redacted]

- [redacted]

9.4 Subgroup Analysis

No subgroup analysis will be performed for the primary efficacy analysis.

10 SAFETY EVALUATION

All safety analyses will be performed on the SAF analysis set.

10.1 Extent of Exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure and compliance and summarized within the safety population.

Duration of IMP exposure

Duration of IMP exposure is defined as last IMP administration date - first IMP administration date + 1, regardless of unplanned intermittent discontinuations. If the date of the last dose of IMP is missing, the duration of IMP will be left as missing.

Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories:

The following summaries will be conducted by treatment group to characterize the exposure to study treatment:

- >0 and ≤ 4 Weeks
- >4 and ≤ 8 Weeks
- >8 and ≤ 12 Weeks
- >12 and ≤ 16 Weeks
- >16 and ≤ 20 Weeks
- ≥ 20 Weeks

Additionally, the cumulative duration of treatment exposure (expressed in participant-months) will be provided.

Treatment compliance

Treatment compliance will be summarized quantitatively and categorically: <80%, ≥80% by treatment group.

10.2 Adverse Events

General common rules for adverse events

All adverse events (AEs) will be coded to a lower-level term (LLT), preferred term (PT), high level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the last Medical Dictionary for Regulatory Activities (MedDRA) version currently available at the time of database lock.

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.
- Treatment-emergent adverse events (TEAE)s: AEs that developed, worsened or became serious during the treatment-emergent period
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period

Similarly, the deaths will be analyzed in the pre-treatment, treatment-emergent and post-treatment periods.

The primary AE analyses will be on TEAEs. Pre-treatment and post-treatment AEs will be described separately.

An AE with incomplete or missing date/time of onset (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment or a post-treatment AE.

Relationship of an AE to study drug will be assessed by the investigator and be given a designation of Not Related, Possibly Related, Probably Related, or Definitely Related in the eCRF. For the purposes of analysis, "Related" will be AEs which are Possibly, Probably, or Definitely Related. If relationship of an AE to study drug is missing, it will be imputed as "Related" for summarization but not imputed in data listings.

Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment phase.

Severity of an AE will be assessed by the investigator and be given a designation of Mild, Moderate, or Severe.

If an AE started the same day as the first dose of study drug, the Adverse Events eCRF field indicating "Before" or "After" will be used to determine if the AE is treatment-emergent.

An AE is considered an Adverse Event of Special Interest (AESI) if it meets one of the criteria as indicated in the study protocol. Analyses of AESI will be based adverse events identified as AESI per medical review.

Infusion-related reactions (IRR) are described in the study protocol. Analyses of infusion-related reactions will be based on categorization per the Adverse Events eCRF field "Is this an Infusion Related Reaction?" = Yes.

The AE tables will be ordered by descending frequency of SOC followed by descending frequency of PT within the PRV-3279 group.

An overall summary of TEAEs by treatment group will be provided for the number and percentage of patients with at least one TEAE in the following categories:

- Any TEAE
- Any TEAE by severity (Mild, Moderate, Severe)
- Any TEAE related to study drug
- Any TEAE leading to permanent discontinuation of PRV-3279
- Any TEAE leading to study discontinuation
- Any serious TEAE
- Any treatment-emergent AESI
- Any IRR
- Any TEAE leading to death

The AE summaries of Table 3 will be generated with number (%) of participants experiencing at least one event.

Table 3 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC and PT
Common TEAE (≥5% in any group)	Primary SOC and PT
TEAE related to IMP as per Investigator's judgment	Primary SOC and PT
TEAE by maximal intensity	Primary SOC and PT
Treatment emergent SAE	Primary SOC and PT
Treatment emergent SAE related to IMP as per Investigator's judgment	Primary SOC and PT
TEAE leading to permanent intervention discontinuation	Primary SOC and PT
TEAE leading to death[b]	Primary SOC and PT
Pretreatment AE	Overview[a] Primary SOC and PT

Type of AE	MedDRA levels
Post-treatment AE	Overview[a]
	Primary SOC and PT
Post-treatment SAE	Primary SOC and PT

a Will include the following AE categories: any AEs, any serious AEs, any AEs leading to death, any AEs leading to permanent intervention discontinuation
b Death as an outcome of the AE as reported by the Investigator in the AE page

Analysis of deaths

In addition to the analyses of deaths included in Table 3 the number (%) of participants in the following categories will be provided:

- Deaths during the treatment-emergent and post-treatment periods
- Deaths in non-randomized or randomized but not treated participants

Analysis of adverse events of special interest (AESIs) and other AEs of interest

Adverse events of special interest (AESIs) and other AEs of interest will be selected for analyses as indicated in Table 4. Number (%) of participants experiencing at least one event will be provided for each event of interest. The risk difference (asymptotic 95% CI with continuity correction) will be computed for PRV-3279 dose versus placebo. Tables will be sorted as indicated in Table 4.

Table 4 - Selections for AESI and other AE of interest

AE Grouping	Selection
severe infections requiring IV antibiotics/antifungal/antiviral and/or hospitalization	CMQ10176 - GLB_INFECTIONS
opportunistic infections related to immune suppression (e.g. pneumocystis carinii etc.)	CMQsn00235 - Opportunistic infections Narrow
herpes zoster	CMQ10162 - GLB_HERPES_ZOSTER
moderate or severe infusion site reactions	CMQ40272 HLT_Infusion site reactions and Severity in (“Moderate”, “Severe”)
anaphylaxis or severe hypersensitivity reaction	CMQsn00021 - Anaphylactic reaction Narrow
	CMQsn00214 - Hypersensitivity Narrow
new malignancy	CMQsn00091– Malignant or unspecified tumors
Thrombosis	CMQsn00081 - Embolic and thrombotic events (SMQ)
MACE (Major Adverse Cardiovascular Events)	Primary SOC= “Cardiac disorders” and PT contain (”myocardial infarction”, ”coronary artery thrombosis”)
	Primary SOC= “Nervous system disorders” and PT contain (” stroke”, ”infarction”, ”thrombosis”,”embolism”)

AE Grouping	Selection
Other selected AE Grouping	
Injection site reaction	CMQ10640 - HLT_Injection site reactions
Infusion related reaction (IRR)	eCRF AE category = "Infusion Related Reaction" and AESI = "Y"

The list of terms may be adjusted according to MedDRA version changes
PT included in each CMQ will be provided by Sponsor

The following summaries will be provided:

All treatment-emergent adverse events, by selected standardized MedDRA query (SMQ) and PT, showing the number (%) of participants with at least 1 PT, sorted by decreasing incidence of PTs within each SMQ in the PRV-3279 treatment group.

For each AESI and other selected AE groupings,

- Number (%) of participants with any specific TEAE
- Number (%) of participants with any specific serious AE (regardless of treatment emergent status)
- Number (%) of participants with any specific treatment emergent serious AE
- Number (%) of participants with any specific AE leading to death
- Number (%) of participants with any specific TEAE leading to study discontinuation
- Number (%) of participants with any specific TEAE related to IMP reported by investigator
- Number (%) of participants with any specific TEAE by maximum intensity
- Number (%) of participants with infusion related reaction
- Number (%) of participants with different number of infusion related reactions.

Information on SAEs is listed by subject.

10.3 Clinical Laboratory Evaluation

The following laboratory variables will be analyzed. They will be converted into standard international units.

- Hematology:
  - Red blood cells and platelets and coagulation: hemoglobin, hematocrit, platelet count, Reticulocyte Count, Absolute, mean corpuscular volume, mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin, red blood cell count
  - White blood cells: white blood cell count, neutrophils, lymphocytes, basophils, eosinophils

- Clinical chemistry:
  - Metabolism: glucose, total protein, albumin, creatine phosphokinase
  - Electrolytes: sodium, potassium, chloride, calcium
  - Renal function: creatinine, blood urea nitrogen
  - Liver function: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total and direct bilirubin
- Urinalysis:
  - Protein/Creatinine, proteins, blood, RBC, WBC, Leukocyte Esterase, Granular Casts, Hyaline Casts, Red Blood Cell Casts, White Blood Cell Casts and Waxy Casts
- Coagulation:
  - activated Partial Thromboplastin (aPTT), Prothombin Time (PT) and International Normalized Ratio (INR)

Quantitative analyses

When relevant, for laboratory variables, descriptive statistics for results and changes from baseline will be provided for each analysis window, the last value during the treatment-emergent period. These analyses will be performed using central measurements only for laboratory variables.

For all parameters, mean changes from baseline with the corresponding standard error will be plotted over time.

Analyses according to PCSA

Potentially clinically significant abnormality (PCSA) analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock. For parameters for which no PCSA criteria are defined, similar analyses will be done using the normal range, if applicable.

Analyses according to PCSA will be performed based on the worst value during the treatment-emergent period, using all measurements (either local or central, either scheduled, nonscheduled or repeated).

For laboratory variables above, the incidence of participants with at least one PCSA during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

10.4 Vital Signs

Summaries of observed value and change from study baseline will be presented for Weight (kg), Systolic Blood Pressure (mmHg), Diastolic Blood Pressure (mmHg), Temperature (°C), Heart Rate (beats/min), and Respiratory Rate (breaths/min) at all nominal visits/timepoints. Results from unscheduled vital signs will not be included in summaries but included in data listings. Supplemental box plots will display observed vital signs results by visit/timepoint and treatment groups.

The number and percentage of patients with a weight decrease >=10% from the study baseline will be presented.

10.5 Physical Examination

A summary table will be produced which will show the number and percentage of subjects by body system who have at least one post-baseline abnormal and clinically significant result.

The results of physical examinations will be presented in a data listing. The data listing will indicate the date of the examination, the body system examined and whether the result of a physical examination was normal, abnormal and not clinically significant, or abnormal and clinically significant. Details will be included for results which are abnormal and clinically significant.

10.6 Electrocardiogram (ECG)

Summaries of observed value and change from baseline will be presented for Heart Rate (beats/min), PR interval (msec), RR interval (msec), QRS Duration (msec), QT interval (msec), and the QTc interval (msec) via Fridericia's correction (QTcF) at all nominal visits. If a patient is missing the QTcF value for an ECG but has available data for the QT interval and RR interval, the QTcF value will be calculated according to the formula:

$$\text{QTcF (msec)} = [\text{QT interval in msec}]/[0.001*\text{RR interval in msec}]^{(1/3)}$$

Results from unscheduled ECGs will not be included in the summaries but included in data listings.

11 OTHER ANALYSES

11.1 Pharmacokinetic Analyses

11.1.1 Data Handling

a) Data rounding specifications for PK data are documented in the PK TLF shells.

   Serum concentrations that are below the limit of quantification (BLQ) will be treated as zero for calculation of concentration descriptive statistics, except for the geometric mean and associated coefficient of variation for which they will be considered as missing.

   For PK analysis, all BLQ values will be treated as zero, with the exception of BLQ values observed between 2 quantifiable concentrations which will be set to missing.

b) Serial blood samples will be collected at the following time points for PK assessment:

   - Days 1 and 141 (for selected patients only): Predose (within 30 minutes), EOI (within 5 minutes), 24±4 hours, 48±4 hours, 72±4 hours, 168±48 hours, and 336±48 hours post-dose
   - Day 1, 29, 57, 86, 113, 141, 169, 197: Pre-dose (within 30 minutes) and within 5 minutes of end of infusion
   - Flare Assessment Visit: As needed
   - End-of-trial (ET) Visit

PK collections that have an actual sampling time that deviates from the predefined collection time windows will be flagged in the data listings and excluded from the calculation of concentration summary statistics.

Individual serum PRV-3279 concentrations will be presented in data listings and summarized separately using descriptive statistics by day and timepoint. Individual serum PRV-3279 concentrations will also be summarized separately by subject ADA status (treatment emergent, non-treatment emergent, or inconclusive) and by ADA titer values. The following descriptive statistics will be presented for serum concentrations obtained at each nominal time point: n, mean, SD, SEM, percent coefficient of variation (CV%), geometric mean (GM), geometric CV% (gCV%), median, minimum, and maximum values.

Individual serum concentrations will be plotted by actual time on both linear and semi-logarithmic scales. Mean serum concentrations will be plotted by day and nominal time on both linear and semi-logarithmic scales. Mean serum concentrations will also be plotted separately by subject ADA status (treatment emergent, non-treatment emergent, or inconclusive).

11.1.2 Serum Pharmacokinetic Parameters

The PK parameters will be calculated using non-compartmental methods from PRV-3279 concentrations using Phoenix® WinNonlin® Version 8.3 or higher (Certara USA, Inc., Princeton, NJ), and will include but may not be limited to those listed in Table 4.

Table 4 - List of PK parameters and definitions

Parameters	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
$t_{1/2}$	Terminal elimination half-life calculated as: $\ln 2/\lambda_z$	Day 1, Day [redacted]
CL	Clearance, calculated as (Dose/$AUC_{0-\infty}$) on Day 1 and as (Dose/$AUC_{[redacted]}$) on Day [redacted]	Day 1, Day [redacted]
V_d	Volume of distribution in terminal phase, calculated as CL/ λ_z	Day 1, Day [redacted]
V_{ss}	Volume of distribution at steady state, calculated as CL*MRT	Day 1, Day [redacted]
MRT	Mean Residence Time, calculated as ($AUMC_{0-\infty}$/$AUC_{0-\infty}$)-(Infusion Length/2) on Day 1 and as (($AUMC_{0-tau}$ + tau($AUC_{0-\infty}$- AUC_{0-tau}))/ AUC_{0-tau})-(Infusion Length/2) on Day [redacted], where $AUMC_{0-\infty}$ and $AUMC_{0-tau}$ are the areas under the first moment curve from time zero to infinity or the dosing interval ([redacted]), respectively, and tau is the dosing interval ([redacted]).	Day 1, Day [redacted]
$RacC_{max}$	Accumulation ratio, C_{max} on Day [redacted]/C_{max} on Day 1	NA
RacAUC	Accumulation ratio, $AUC_{[redacted]}$ on Day [redacted]/$AUC_{[redacted]}$ on Day 1	NA

In addition to the above PK parameters, which will be listed and summarized, the following parameters will also be listed to document the selection of data points used to estimate $t_{1/2}$ using non-compartmental procedures:

Parameters	Definition	Time Point
λ_z	Apparent terminal elimination rate constant, where λ_z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase.	Day 1, Day [redacted]
Number points	Number of data points used to estimate λ_z; a minimum of 3 data points must be used, and C_{max} must not be included.	Day 1, Day [redacted]
λ_z lower	Lower bound used for the estimation of λ_z.	Day 1, Day [redacted]
λ_z upper	Upper bound used for the estimation of λ_z.	Day 1, Day [redacted]

Parameters	Definition	Time Point
Span	Number of elapsed half-lives over which λ_z is estimated, calculated as: (λ_z upper – λ_z lower) / $t_{½}$.	Day 1, Da [redacted]
Rsq	r^2, the coefficient of determination (goodness of fit statistic); λ_z and all associated parameters will be flagged and excluded from summary statistics where $r^2 < 0.80$.	Day 1, Da
$\%AUC_{ext}$	Percentage of AUC_{inf} due to extrapolation; $AUC_{0-\infty}$, CL and V_d values will be flagged and excluded from summary statistics where $\%AUC_{ext} > 20\%$.	Day 1

These PK parameters will be presented in data listings and summarized by day on the PK analysis set using the following descriptive statistics: n, mean, SD, CV%, GM, gCV%, median, minimum, and maximum values. T_{max} will be summarized using number of observations, median, minimum, and maximum only. PK parameters will also be summarized by subject ADA status (treatment emergent, non-treatment emergent, or inconclusive).

11.1.3 Accumulation ratio

For C_{max} and AUC individual accumulation ratio Rac C_{max} and Rac AUC at Day [redacted] will be calculated as C_{max} at Day [redacted]/C_{max} at Day 1 and AUC at Day [redacted]/AUC at Day 1.

Accumulation ratio Rac C_{max} and Rac AUC at Day [redacted] and 90% CI for the PRV-3279 10 mg/kg group will be calculated.

A listings of individual accumulation ratios will be provided, along with their descriptive statistics (n,mean, SD, CV%, GM, gCV%, median, minimum and maximum).

11.1.4 Steady-state

Steady state on Ctrough will be assessed using a nonlinear mixed model (Hoffman et al, 2005):

$$C_{ij} = C_{ss}e^{c_i}(1 - e^{-(\gamma e^{g_i} j)})e^{\varepsilon_{ij}}$$

where C_{ij} is the observed trough (C_{trough}) plasma concentration for the i^{th} subject on Day j, C_{SS} is the average steady state trough (C_{trough}) plasma concentration, γ is the average first-order elimination rate, $\varepsilon_{ij} \sim N(0, \sigma^2_e)$ is the random within-subject error, and c_i and g_i are the random individual deviations from C_{ss} and γ, respectively, such that

$(c_i, g_i) \sim N([0, 0], \Sigma)$ with

$$\Sigma = \begin{bmatrix} \sigma_c^2 & \sigma_{cg} \\ \sigma_{cg} & \sigma_g^2 \end{bmatrix}$$

The model assumes a log-normal distribution for both the within-subject erros (ε_{ij}) and the random effects c_i and g_i. The above nonlinear model analysis will be based on the log-transformed C_{min} values. Data from all subjects together from all dose groups will be used for the analysis.

Time (t_{ss} in days) at which 90% of the subject-specific C_{ss} is achieved (ie, individual steady state attainment) will be calculated from the model, using the equation:

$$t_{ss} = \frac{\log(1 - 0.9)}{-\gamma}$$

Similarly, time (in days) at which 50% of the subject-specific C_{ss} is achieved (ie, average steady state attainment) will also be provided.

In addition, model parameter estimates with standard errors and 90% CIs will be provided. The adequacy of the nonlinear model will be assessed graphically by plotting residual versus dose, residual versus time, and observed (log-scale) and predicted values versus time for individual subjects.

11.2 Immunogenicity Analyses

Participant's ADA status, response variable and kinetics of ADA responses (see definitions below) will be summarized on the ADA immunogenicity analysis set for anti- PRV-3279 antibodies.

Kinetics of ADA responses will be described for participants with treatment-induced ADA and for participants with treatment-boosted ADA, separately. Time to ADA onset and duration of ADA will be described with minimum, Q1, median, Q3 and maximum statistics.

Peak titer will be described with minimum, Q1, median, Q3 and maximum statistics for participants with treatment-induced ADA and for participants with treatment-boosted ADA, separately.

Sample status (negative, positive, inconclusive) and titers will also be described overtime using descriptive statistics.

The impact of positive immune response on efficacy, PK and safety variables may be further explored, depending on ADA incidence.

Participant's ADA status

- Participants with **pre-existing ADA**s correspond to participants with ADAs present in samples drawn before first administration of intervention. Participants with missing ADA sample at baseline will be considered as without pre-existing ADA.

- Participants with **treatment-emergent ADA** correspond to participants with at least one treatment-induced/boosted ADA at any time after first IMP administration.
  - Participants with **treatment-induced ADA**s correspond to participants with ADAs that developed at any time after first IMP administration and without pre-existing ADA (including participants without pre-treatment samples).
  - Participants with **treatment-boosted ADA**s correspond to participants with pre-existing ADAs that are boosted during the TE period to a significant higher titer than the baseline. A 3-fold serial dilution schema is used during titration, so at least a 9-fold increase will be considered as significant.
- Participants **without treatment-emergent ADA** correspond to participants without treatment-induced/boosted ADA and without any inconclusive sample at any time after first IMP administration.
- Participants with unclassified ADA correspond to participants with pre-existing ADAs that cannot be classified as treatment-boosted ADA because of missing titer(s) (ie, a positive ADA sample at any time after first IMP administration in a participant with pre-existing ADA but with missing titer at this sample or at baseline).
- Participants **with inconclusive ADA** are defined as participants which cannot irrefutably be classified as with or without treatment-emergent ADA.

Kinetics of ADA response

Kinetics of ADA response will be derived for participants with treatment-induced/boosted ADA considering ADA samples collected during the TE period and post-treatment period.

- **Time to onset of ADA response** is defined as the time period between the first IMP administration and the first treatment-induced/boosted ADA.
- **Duration of ADA response** is defined as the time between the first treatment-induced/ boosted ADA and the last treatment-induced/boosted ADA, irrespective of negative samples or positive samples not reaching the boosted threshold in-between. ADA duration will be summarized only for participants with persistent ADA response.
- **Persistent ADA response** is defined by treatment-induced/boosted ADA with a duration of ADA response of at least 16 weeks.
- **Transient ADA response** is defined by treatment-induced/boosted ADA with a duration of ADA response duration of less than 16 weeks and the last sample is not treatment-induced/boosted.
- **Indeterminate ADA response** is defined by treatment-induced/boosted ADA that are neither persistent nor transient.

ADA response variable:

- **ADA incidence:** is defined as the proportion of participants found to have seroconverted (treatment-induced ADAs) or boosted their pre-existing ADA response (treatment-boosted ADAs) at any time point after first IMP administration.

11.3 Pharmacodynamic Markers

By-visit descriptive summaries of results pertaining to PD markers as below and relationships to other study endpoints, may be conducted as an exploratory analysis on the PD analysis set.

11.3.1 SLE Serology and Disease Activity Markers

By-visit descriptive summaries of the following SLE serology and disease activity markers will be produced:

- 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

Relationships to other study endpoints may be conducted as an exploratory analysis.

11.3.2 TBNK Panel

By-visit descriptive summaries of results from the TBNK panel (T, B NK cells and other subsets) will be produced. Relationships to other study endpoints may be conducted as an exploratory analysis.

11.3.3 [redacted]

[redacted]

11.4 Receptor Occupancy

By-visit descriptive summaries of results pertaining to receptor occupancy analysis will be produced on the PK analysis set. Relationships to pharmacokinetic and other study endpoints may be conducted as an exploratory analysis

No receptor occupancy analyses will be conducted for China.

11.5 Changes to the Planned Analysis

This section is to document any changes from the planned analyses described in the study protocol. Changes will be finalized in the final SAP prior to database lock.

For Laboratory parameters, PSCA criteria will be used instead of PCI criteria to match with Sponsor standard.

12 REFERENCES

1) Ruperto N, Hanrahan L, Alarcón G, et al. International consensus for a definition of disease flare in lupus. Lupus. 2011; 20:453-62.
2) Merrill JT, June J, Koumpouras R et al. Top-line results of a Phase 2 trial of a reversible B Cell inhibitor, Xmab 5871. 2018; SLE ACR 2018: abstract L7.
3) Health Outcomes™ Scoring Software 5.0. Lincoln, RI, QualityMetric Incorporated 2016.

13 APPENDICES

13.1 Schedule of Activities

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]											
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
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).
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.

[redacted]

13.2 FACIT-F Subscale Score Calculation

The FACIT-F contains 13 items with each item's individual score ranging from 0 (Not at all) to 4 (Very much). The instructions for obtaining the FACIT-F subscale score are as follows:

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

Instructions: *
1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. **The higher the score, the better the QOL.**

Subscale	Item Code	Reverse item?		Item response	Item Score
FATIGUE	HI7	4	-	_____	=_____
SUBSCALE	HI12	4	-	_____	=_____
	An1	4	-	_____	=_____
	An2	4	-	_____	=_____
Score range: 0-52	An3	4	-	_____	=_____
	An4	4	-	_____	=_____
	An5	0	+	_____	=_____
	An7	0	+	_____	=_____
	An8	4	-	_____	=_____
	An12	4	-	_____	=_____
	An14	4	-	_____	=_____
	An15	4	-	_____	=_____
	An16	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 13: _____
Divide by number of items answered: _____=**Fatigue Subscale score**

13.3 PCS Score Calculation

Information in this appendix come from the QualityMetric Health Outcomes™ Scoring Software 5.0 User Guide.

The SF-36v2® Health Survey contains 36 items used to measure eight scales of health-related quality of life. The items and the scales are related as shown below.

Scale	Number of items	Items from SF-36[1]
Physical Functioning	10	3, 4, 5, 6, 7, 8, 9, 10, 11, 12
Role Limitations due to Physical Health	4	13, 14, 15, 16
Bodily Pain	2	21, 22
General Health Perceptions	5	1, 33, 34, 35, 36
Vitality	4	23, 27, 29, 31
Social Functioning	2	20, 32
Role Limitations due to Emotional Problems	3	17, 18, 19
Mental Health	5	24, 25, 26, 28, 30

[1] Item 2 is not listed as it is not used to measure scales.

Step 1. Data Cleaning and Item Recoding

Any values that are outside the range of acceptable item response values are converted to missing values. Items 1, 20, 21, 22, 23, 26, 27, 30, 34, and 36 are reversed so that a higher item response value indicates better health.

Step 2. Item Recalibration

Items 1, 21 and 22 require recalibration to satisfy the assumption of a linear relationship between the item scores and the underlying health concept defined by their scales. The recalibration is described below.

Response to Item 1	Recalibrated Value
Excellent	5.0
Very good	4.4
Good	3.4
Fair	2.0
Poor	1.0

Response to Item 21	Recalibrated Value
None	6.0
Very mild	5.4
Mild	4.2
Moderate	3.1
Severe	2.2
Very severe	1.0

Response to Item 22	Response to Item 21	Item 22 Recalibrated Value
Not at all	Missing	6.0
A little bit	Missing	4.75
Moderately	Missing	3.5
Quite a bit	Missing	2.25
Extremely	Missing	1.0
Not at all	None	6
Not at all	Very mild to Very severe	5
A little bit	Any	4
Moderately	Any	3
Quite a bit	Any	2
Extremely	Any	1

Step 3. Computation of Raw Scores

A raw score is computed for each scalre. This score is the simple algebraic sum of the final values for all items in that scale.

Step 4. Transformation of Raw Scale Scores to 0-100 Scores

The lowest and highest possible scores are transformed to zero and 100, respectively. Scores between these values represent the percentage of the total possible score achieved.

Step 5. Standardization of the SF-36v2® Health Survey Scales

Each scale is standardized using a z-score transformation. The z-score for each scale is computed by subtracting the mean 0-100 score observed in the 1998 general U.S. population from 0-100 score of each scale and dividing the difference by the corresponding scale standard deviation observed in the 1998 general U.S. population.

Step 6. Aggregation of the Scale Scores

An aggregate physical score is computed by multiplying the z-score of each scale by its associated physical factor score coefficient derived from the 1990 general U.S. population, and summing the eight products. If any of the scale scores are missing, then the aggregate physical score is not computed.

Step 7. Transformation of Summary Scores

The aggregate physical summary score is transformed to the T-score Based (50, 10) scoring. This is done by multiplying the aggregate summary score by 10 and adding the resulting product to 50.

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Approve & eSign	[redacted] Clinical [redacted]

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