STATISTICAL ANALYSIS PLAN

Protocol Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study Evaluating the Efficacy and Safety of Daxdilimab in Adult Participants with Active Proliferative Lupus Nephritis
Name of Test Drug:	Daxdilimab (HZN-7734)
Protocol Number:	HZNP-DAX-203
Protocol Version (Date):	17-May-2022
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ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CI	Confidence interval
COA	clinical outcome assessment
CRR	complete renal response
CSR	clinical trial report
eGFR	estimated glomerular filtration rate
IFN	interferon
LN	lupus nephritis
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMF/MPA	Mycophenolate Mofetil/Mycophenolic Acid
MMRM	mixed model for repeated measures
mSFI	modified SELENA-SLEDAI Flare Index
MxA	myxovirus resistance protein A
OCS	oral corticosteroids
PD	pharmacodynamics
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PK	pharmacokinetics
PRO	patient report outcome
PRR	Partial renal response
PT	preferred term
[redacted]	[redacted]
Q1, Q3	first quartile, third quartile
[redacted]	
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event

SAP	statistical analysis plan
SAS	Statistical Analysis Software
SC	subcutaneously
SD	standard deviation
SDI	Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index
SE	Standard error
SFU	Safety Follow-Up
SLE	systemic lupus erythematosus
[redacted]	[redacted]
SLICC/ACR	Systemic Lupus International Collaborating Clinics/American College of Rheumatology
SOC	system organ class
SPP	statistical programming plan
TEAE	treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse events
TEAESI	treatment-emergent adverse events of special interest
VAS	visual analog scale
ULN	upper limit of normal
UPCR	urine protein to creatinine ratio
WHO-DD	World Health Organization Drug dictionary

SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision
31 JAN 2023			Initial Draft

1 INTRODUCTION

This document describes the statistical analysis for protocol "HZNP-DAX-203, a multicenter, randomized, double-blind, placebo-controlled, phase 2 study evaluating the efficacy and safety of daxdilimab in adult participants with active proliferative lupus nephritis". Standard data presentation instructions, and table, figure, and listing specifications are contained in the Statistical Programming Plan (SPP) in a separate document.

There are three planned analyses for this study, which include the primary efficacy and safety analysis at Week 52, the final analysis at Week 112 and an [redacted].

2 TRIAL OVERVIEW

2.1 Trial Objectives and Endpoints

The objectives and corresponding endpoints are listed in Table 1 below:

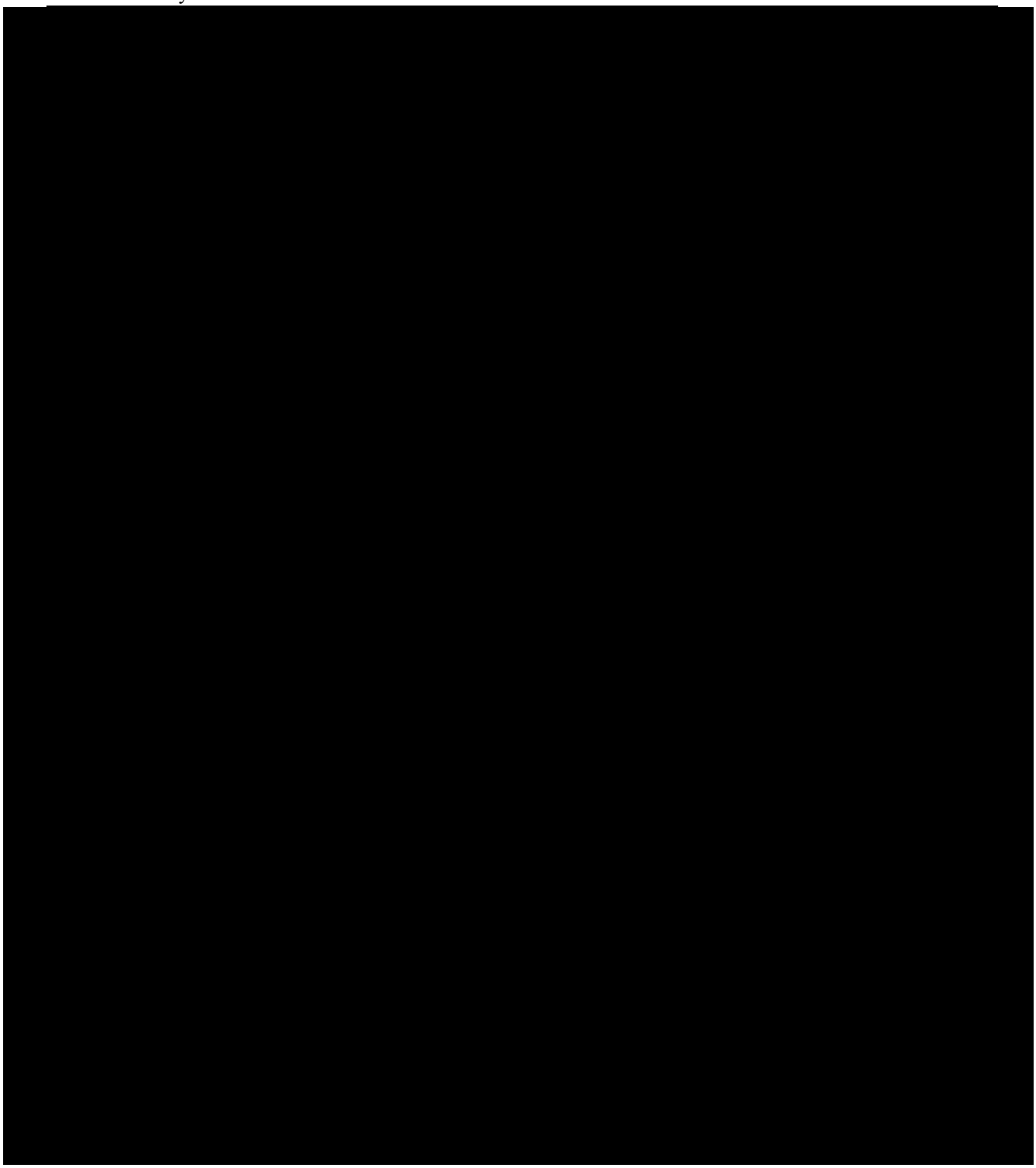
Table 1 Trial Objectives and Endpoints

Primary Objective	**Primary Endpoint**
To evaluate the efficacy of daxdilimab in combination with SOC compared to placebo in combination with SOC in participants with active, proliferative LN	Complete Renal Response (CRR) at Week 48 and sustained through Week 52. CRR is defined as meeting all of the following criteria: • Estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73m^2 or no worse than 15% below baseline • 24-hour UPCR ≤ 0.5 mg/mg • No discontinuation of study intervention or use of restricted medication beyond the protocol allowed threshold before assessment
Secondary Objectives	**Secondary Endpoints**
To assess overall renal response (ORR) with daxdilimab versus placebo in participants with active, proliferative LN	ORR (defined as CRR or partial renal response (PRR)) at Week 48 and sustained through Week 52 See above for definition of CRR. PRR is defined as meeting all of the following criteria: • eGFR ≥ 60 mL/min/1.73m^2 or no worse than 15% below baseline • Improvement in 24-hour UPCR: o For participants with a baseline UPCR ≤ 3.0 mg/mg: < 1.0 mg/mg o For participants with a baseline UPCR > 3.0 mg/mg: > 50% improvement from baseline and ≤ 3.0 mg/mg • No discontinuation of study intervention or use of restricted medication beyond the protocol allowed threshold before assessment
To assess the change from baseline in eGFR with daxdilimab versus placebo in participants with active, proliferative LN	▪ Change from baseline in eGFR at Week 52
To evaluate the ability to improve dose requirements of oral corticosteroids (OCS) with daxdilimab versus placebo in participants with active, proliferative LN.	Able to taper OCS to ≤ 2.5 mg/day prednisone-equivalent by Week 24 and maintain this dose through Week 52. Sustained reduction of OCS dose: ▪ Prednisone-equivalent dose ≤ 2.5 mg/day by Week 24 and not exceeding this dose through Week 52 and ▪ No discontinuation of study intervention or use of restricted medication beyond the protocol allowed threshold before assessment
To characterize the PK and immunogenicity of daxdilimab in participants with active, proliferative LN.	• Serum concentration of daxdilimab over time. • Rate of ADA directed against daxdilimab and ADA titer for the duration of the study.

Table 1 Trial Objectives and Endpoints

To evaluate the safety and tolerability of daxdilimab in combination with SOC in participants with active, proliferative LN.	• Incidence of treatment-emergent adverse events (TEAEs) over time. • Incidence of treatment-emergent serious adverse events (TESAEs) over time. • Incidence of treatment-emergent AEs of special interest (TEAESIs) over time: hypersensitivity reaction, including anaphylaxis, severe (Grade 3 or higher) viral infection/reactivation, herpes zoster, opportunistic infection, and malignancy (except non-melanoma skin cancer).
[redacted]	[redacted]

[redacted]



[redacted]

2.2 Trial Design

This trial is a Phase 2, multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to assess the efficacy and safety of daxdilimab in patients with active, proliferative lupus nephritis despite standard of care.

Approximately 210 participants will be randomized in a ratio of 1:1:1 (70 participants per group) to receive either daxdilimab [redacted] mg or [redacted] mg SC or placebo SC in addition to SOC background therapy as described below in Table 2. Randomization will be stratified by:

- Pre-randomization urine protein to creatinine ratio (UPCR) < 3.0 mg/mg vs. ≥ 3.0 mg/mg
- Screening eGFR < 60 mL/min/1.73m^2 vs. ≥ 60 mL/min/1.73m^2

Table 2 Stage I Treatment Assignment

[redacted]

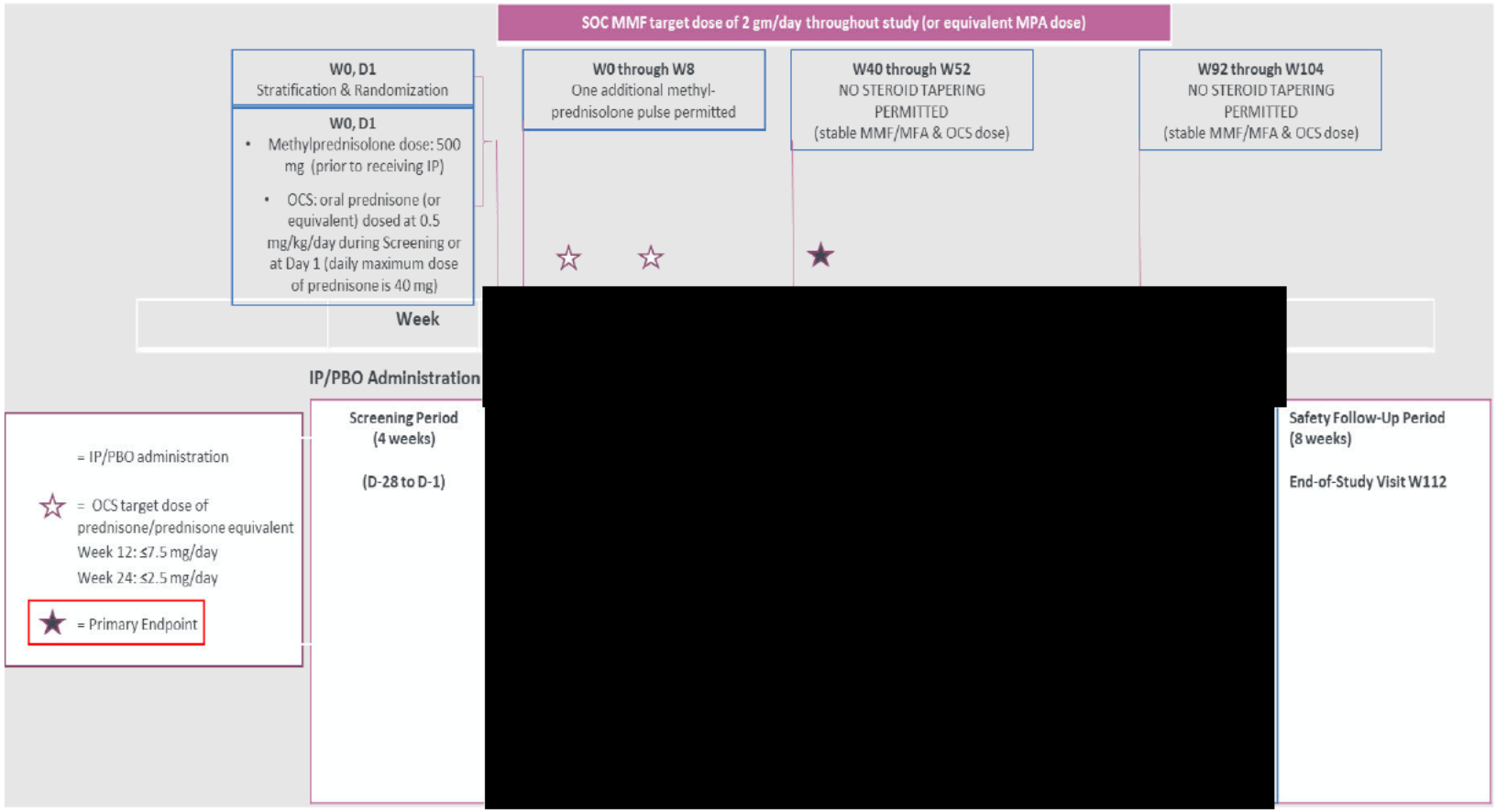
[redacted]

Table 3 Stage II Treatment Assignment

[redacted]

The basic study flow diagram is presented in Figure 1

Figure 1 Study Flow Diagram



CRR = complete renal response; D = day; IP = investigational product; MMF = mycophenolate mofetil; MPA = mycophenolic acid; OCS = oral corticosteroids; PRR = partial renal response; [redacted] SC = subcutaneously; SFU = Safety Follow-Up; SOC = standard-of-care; W = week.

2.3 Sample Size

A sample size of approximately 210 participants (up to approximately 70 participants per treatment group) is planned for this trial. The sample size was calculated based on the primary efficacy endpoint. Assuming a placebo response rate of 25%, 70 participants per treatment group will provide approximately 80% power to detect an increase in response of 20% in either arm of a daxdilimab group as compared to the placebo group at the 2-sided alpha level of 0.10 using a Chi-square test. The minimum detectable difference is 13% between the daxdilimab group and placebo group. The assumption of 25% responder rate for placebo is based upon published results (Mejia-Vilet et al., 2021).

3 PLANNED ANALYSES

[redacted]

3.2 Planned Primary Analysis

The primary analysis will be conducted after the last participant has completed the Week 52 Visit or discontinued from study early. For the primary analysis, all the efficacy and safety data collected prior to the data cut-off will be analyzed.

3.3 Planned Final Analysis

The final analysis will be conducted after all participants have completed Week 112 Visit or discontinued early from the study.

4 STATISTICAL METHODS

4.1 General Considerations for Data Analyses

All statistical calculations will be primarily performed using SAS® System Version 9.4 or higher (SAS Institute Inc., Cary, NC, USA).

The primary comparison will be between the daxdilimab [redacted] mg or [redacted] mg group and the placebo group. For primary and second efficacy analyses, the data up to the [redacted] Visit will be used. The applied methods for statistical descriptive analysis and presentations will be based on the types of variables being tested.

1) Overall summary of descriptive statistics for continuous variables will include, not limited to, the number of observations, mean, standard deviation, median, minimum, and maximum, first quartile, and third quartile values in each treatment group
2) Overall summary of descriptive statistics for categorical variables will include, not limited to, frequency counts, percentage of patients of point estimate

Data summaries for Stage I of the Treatment Period will be presented by randomized treatment group (i.e., "daxdilimab [redacted] mg", "daxdilimab [redacted] mg" and "Placebo") and overall. Data summaries for Treatment Period Stage II (i.e., the Stage II period beginning at the [redacted] Visit) will be presented according to the reassigned treatment regimen with respect to achievement of PRR (or CRR) at Weeks 48 and maintained through Week 52 (e.g., "daxdilimab [redacted] mg [redacted] mg [redacted]", "daxdilimab [redacted] mg [redacted] mg [redacted]", "daxdilimab [redacted] mg [redacted] mg [redacted]", "Placebo [redacted]/Placebo [redacted]", and "Placebo [redacted]/daxdilimab [redacted] mg [redacted]"). For the longitudinal analysis covering two-stage periods (Stage I and Stage II) of treatment, participants will be analyzed according to the combination of treatment that they actually received in Stage I and Stage II treatment period.

Summaries of study and participant characteristics (e.g., demographics and baseline characteristics, medical history, protocol deviations) will be reported.

For additional details on data presentation, refer to the Statistical Programming Plan (SPP).

Table 4 provides the overview of the study periods for reporting purposes. All major analysis endpoints will be reported for Stage I and Stage II. All assessments, unless otherwise specified, will be included in by-patient listings. Data collected at unscheduled visits may be used in the data analysis and will not be presented in the summary statistics report.

Table 4 Study Periods

Study Period	Description
Stage I	Day 1 to [redacted] trial intervention administration and safety/efficacy assessments
Stage II	Post [redacted] trial intervention administration and safety/efficacy assessments + safety follow-up

4.1.1 Definition of Baseline

Unless otherwise specified, baseline is defined as the last non-missing valid observation prior to the first dose of trial intervention. In cases where baseline measurements are taken on the same day as trial intervention and no times are reported, it will be assumed that these measurements are taken prior to trial intervention being administered.

At [redacted] participants from all three Treatment Groups will be assigned to a [redacted] based upon the renal response observed at [redacted] All participants who did not achieve the primary endpoint will be re-baselined at [redacted]. A re-baseline is defined as the last available assessment prior to the first quarterly dose of study intervention administered at [redacted]

4.1.2 Analysis Windows

Analysis visit windows will be used for all visit-based assessments to map longitudinal observations to scheduled visits and thereby allow for by-visit analyses, since not all assessments are performed on the scheduled day. Unless otherwise specified, all longitudinal efficacy, safety, and [redacted] will be based on the analysis visit windows. The analysis visit windows will be calculated by bisecting the interval between adjacent scheduled visit days except for the first post-treatment visit and the [redacted] visit. The first post-treatment visit will start at Day 2. When mapping to the [redacted] analysis window, this should only occur for assessments on or before the date of the nominal [redacted] dosing. Assessments after this date will be mapped to the following analysis visit windows. The detailed analysis visit windows will be specified in the SPP. The actual assessment day will be mapped to the windows defined for each scheduled study visit by the following rules:

- If more than one assessment falls within a visit window, the closest non-missing assessment to the scheduled day will be used in the analysis.
- If 2 non-missing assessment actual dates are equidistant from the target day, the later visit will be used in the analysis.
- For retest values of laboratory data, the retest value will be chosen.

4.1.3 Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified.

4.2 Protocol Deviations

- The protocol deviations are reviewed and categorized as significant and non-significant prior to the database lock.

    - Significant protocol deviation: a protocol deviation that affects primary efficacy and safety assessments (as applicable), the safety or mental integrity of a subject, or the scientific value of the project.

- Non-significant protocol deviation: a protocol deviation that is identified but does not impact the endpoints (as applicable), the safety or mental integrity of a subject, or the scientific value of the project.

All the protocol deviations will be listed. The number and percentage of participants with significant protocol deviations by deviation reason (e.g., nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized.

A by-participant listing will be provided for those participants who did not meet at least one eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than one deviation) that participants did not meet and related comments, if collected.

4.3 Statistical Hypotheses

The statistical hypotheses are as follows:

- Null hypothesis (H0): difference in proportion of CRR responders (daxdilimab vs placebo) = 0
- Alternative hypothesis (Ha): difference in proportion of CRR responders (daxdilimab vs placebo) ≠ 0

4.4 Analysis Sets

4.4.1 Full Analysis Set

The Full Analysis Set will include all randomized participants who receive any dose of trial intervention in the study. Participants will be analyzed according to the treatment randomized. The efficacy analysis will be based on the Full Analysis Set.

4.4.2 Safety Analysis Set

Safety Analysis Set will include all participants who receive any dose of trial intervention in the study. Participants will be analyzed according to the treatment that they actually received. Safety, PD, and ADA analyses will be based on the Safety Analysis Set.

4.4.3 Pharmacokinetic (PK) Analysis Set

The PK Analysis Set will include all participants who receive any dose of daxdilimab in the study and have at least one quantifiable serum PK observation post first dose. Participants will be analyzed according to the treatment that they actually received. The PK analysis will be based on the PK Analysis Set

4.4.4 Stage II Analysis Set

The stage II analysis set includes all participants who received at least one dose of trial intervention during the Stage II treatment period starting from [redacted].

4.4.5 Any Daxdilimab Set

The any daxdilimab analysis set includes all participants who receive at least one dose of daxdilimab during the trial.

4.5 Participant Disposition

A summary of participant disposition will be presented into two sections:

- Stage I
- Stage II

In Stage I section, the participants will be presented using the categories presented below.

- Screened
- Screen failed with reasons
- Randomized
- Randomized but not treated
- Randomized and treated
- Completed Stage I treatment
- Discontinued Stage I treatment with reasons
- Completed Stage I trial
- Discontinued Stage I trial with reasons

In Stage II section, the participants be presented using the categories presented below.

- Participants entered into Stage II trial
- Completed Stage II treatment
- Discontinued Stage II treatment with reasons
- Completed Stage II trial
- Discontinued Stage II trial with reasons

4.6 Trial Intervention Exposure

- The number of doses received, amount of the trial intervention received, total number of doses planned per protocol, durations of the trial intervention exposure, and treatment compliance will be summarized by treatment groups. For treatment compliance, the number and proportion of patients who had treatment compliance percentage in range by increments of 10% (i.e., >= 90% to <= 100%; >= 80% to < 90%; >= 70% to < 80% etc.) during treatment period will also be summarized by treatment groups. The summary will be produced using the Full Analysis Set for Stage I, Stage II and overall study. Duration of the trial intervention exposure is defined as follows:
  - Stage I: [redacted] dose date – first dose date
  - Stage II: last dose date + 28 – [redacted] dose date + 1

- The amount of trial intervention exposure: if a participant received a partial dose at a dosing visit, then the amount of trial intervention at that dosing visit will be estimated based on the actual volume administered.
- Treatment compliance for an individual participant = [Total number of doses received]/[Total number of doses planned per protocol] ×100%.

In addition, the total number of participants with missed doses and reasons for missed dose will be summarized by randomized treatment group and overall.

4.7 Demographics, Baseline Characteristics, and Medical History

The demographics (age, gender, race, ethnicity, height, weight, and body mass index) will be summarized by randomized treatment group and overall using the Full Analysis Set. Participant listings of these data will also be provided.

A summary of baseline disease characteristics, by randomized treatment group and overall, for the Full Analysis Set will include:

- Time from first diagnosis of proliferative LN based on a renal biopsy at baseline (baseline renal biopsy may be obtained within 6 months prior to signing the informed consent form (ICF) or during the Screening Period)
- Pre-randomization urine protein to creatinine ratio (UPCR) (< 3.0 mg/mg vs ≥ 3.0 mg/mg) (if more than one UPCR measurements available, use the last valid measurement),
- Screening estimated glomerular filtration rate (eGFR) (< 60 mL/min/1.73m^2 vs ≥ 60 mL/min/1.73m^2),
- eGFR (calculated by the MDRD formula),
- 24-hour UPCR,
- Renal-biopsy lupus nephritis class (Class III (± class V) vs class IV (± class V)),
- [redacted]
- The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI),
- [redacted]
- [redacted]
- Baseline OCS use (yes vs. no),
- Baseline OCS dose (≤7.5 mg/day vs >7.5 mg/day),
- Baseline MMF/MPA use (yes vs. no),
- Baseline MMF/MPA dose (≤ 2 gm/day vs > 2 gm/day),
- [redacted]

- Antinuclear antibodies (ANA) ≥ 1:80 (yes vs. no),
- [redacted]
- [redacted]
- [redacted]

Significant medical history findings will be summarized by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) (Version 23 or later), by randomized treatment group and overall.

4.8 Efficacy Analyses

4.8.1 Primary Efficacy Endpoint and Analysis

4.8.1.1 Primary Efficacy Endpoint and Estimand

The estimand of primary interest is defined as follows, using composite variable strategy to address intercurrent events: participants for receipt of rescue therapy or treatment discontinuation will be treated as failure to meet CRR and considered as non-responder. For participants who experience multiple intercurrent events, data will be handled according to the first intercurrent event.

1. Population: Participants in the Full Analysis Set
2. Variable (endpoint measure): CRR at Week 48 and sustained through Week 52. CRR is defined by meeting all of the following criteria:
    i. eGFR ≥ 60 mL/min/1.73m^2 or no worse than 15% below baseline.
    ii. 24-hour UPCR ≤ 0.5 mg/mg.
    iii. No use of restricted medication beyond the protocol allowed threshold before assessment.
    iv. No discontinuation of study intervention
3. Intercurrent event:
    a. Rescue medications: Captured in the primary variable definition.
    b. Treatment discontinuation: Captured in the primary variable definition.
4. Population-level summary: Difference in proportions of responders between the daxdilimab group and placebo group (daxdilimab [redacted] mg or [redacted] mg vs. placebo)

4.8.1.2 Primary Efficacy Analysis

The proportion of participants achieving CRR at Week 48 and sustained through Week 52 in the daxdilimab group will be compared to that of the placebo group using a logistic regression model with treatment, adjusting for baseline eGFR value and baseline 24-hour UPCR value in the model using the full analysis set. The baseline 24-hour UPCR will be derived using the urine sample collected at Week 0 (Day 1) prior to randomization and administration of first dose of study intervention. Baseline eGFR will be based on the measurement available prior to the first dose of study intervention. The

difference in proportions of responders of daxdilimab vs placebo will be estimated together with its associated 2-sided 90% confidence interval (CI). Longitudinal presentations of results over time up to [redacted] based on the same analysis will be created. A bar chart will also be provided showing the proportion of participants meeting the criteria for CRR and individual components of CRR at Week 48 and maintained through Week 52 by treatment groups. A line plot over time will also be produced by treatment groups.

4.8.1.3 Subgroup analyses of primary endpoint

The following subgroups will be investigated for the primary endpoint:

- Renal-biopsy lupus nephritis class -- the World Health Organization (WHO) or 2003 ISN/RPS classification (Class III (± class V) vs. class IV (± class V))
- Gender (male vs. female)
- Race (white, black or African American, and other)
- Ethnicity (Hispanic/Latino vs. not Hispanic/Latino)
- Baseline IFN gene signature (high vs. low)
- Age group (<65 vs. ≥65)
- Region (North America + Western Europe vs. rest of the world)
- ADA positive at any time (yes vs. no)
- Pre-randomization urine protein to creatinine ratio (UPCR) (< 3.0 mg/mg vs. ≥ 3.0 mg/mg)
- Screening estimated glomerular filtration rate (eGFR) (< 60 mL/min/1.73m^2 vs. ≥ 60 mL/min/1.73m^2)

The nominal p-value and 90% CIs of treatment effect will be provided for each subgroup analysis. Given that the number of participants in some subgroups may be limited, subgroup categories may be combined as appropriate. Otherwise, the subgroup analysis may not be performed if deemed infeasible based on sample size.

Forest plots will be generated to visually present the consistency of treatment effect in different subgroups with overall treatment effect. Other subgroup analyses may be explored as needed.

4.8.1.4 Control of Type I Error

1. The type I error rate will be controlled at a 0.1 level (2-sided) for the primary efficacy analysis using a fixed sequence testing procedure. The primary endpoint will be tested for daxdilimab [redacted] mg compared with placebo.
2. If p-value is ≤ 0.1 in step 1, the primary endpoint will be tested for daxdilimab [redacted]mg compared with placebo. If step 1 test is not significant, the test for Daxdilimab [redacted] mg will not be performed.

4.8.1.5 Sensitivity Analysis

Race and ISN/RPS lupus nephritis disease class have been shown to be associated with poor prognosis and responses to treatment in patients with LN. A sensitivity analysis for

the primary endpoint with race and ISN/RPS classification included as additional covariates in the logistic regression model as defined in 4.8.1.2 will be performed to adjust the potential imbalance across treatment groups.

4.8.1.6 Supplementary Analyses of the Primary Efficacy Endpoint

Supplementary analyses will be performed using the same logistic regression model as the primary analysis (section 4.8.1.2) based on Stage I data using the full analysis set. These supplementary analyses provide additional insights for primary efficacy results. Treatment policy will be used to handle rescue medication use and treatment discontinuation, i.e., including all observed data collected after rescue medication administration and treatment discontinuation regardless of receipt of rescue therapy or treatment discontinuation.

The proportion of subjects that achieved CRR at Week 48 but not at Week 52 will be computed by randomized treatment group using the Full Analysis Data Set.

4.8.1.7 Handling Plan for Missing Data

4.8.1.7.1 Imputation if Missing a Single Lab Component within a Visit

The 24-hour UPCR and eGFR values will be used for the primary efficacy endpoint evaluation. No imputation will be performed for missing baseline values. If either the 24-hour UPCR or eGFR is missing at a single treatment visit,

- the missing 24-hour UPCR will be imputed using the observed spot UPCR from the same visit unless a 24-hour UPCR can be obtained from a recent unscheduled visit (e.g., within maximum 4-week period), then the 24-hour UPCR from this unscheduled visit will be used. Otherwise, the 24-hour UPCR will be imputed using Last Observation Carried Forward (LOCF) of the most recent scheduled measurement of 24-hour UPCR if available or spot UPCR when 24-hour UPCR is unavailable.
- the missing eGFR will be imputed using LOCF.

4.8.1.7.2 Imputation for Missing Data

The intermittent missing data will be imputed using LOCF. Participants with missing outcomes due to early discontinuation from the study will be considered as non-responders.

4.8.2 Secondary Efficacy Endpoints and Analyses

4.8.2.1 Secondary Efficacy Endpoints and Estimands

The estimand for the binary secondary efficacy endpoints is defined as follows, using composite variable strategy to address intercurrent events.

1. Population:

a. ORR: Participants in the Full Analysis Set.
b. Sustained reduction of oral corticosteroids (OCS) dose: Participants in the Full Analysis Set whose Baseline OCS dose is greater than 2.5 mg/day prednisone equivalent (Appendix 1).

2. Variables (outcome measures):

   a. ORR at Week 48 and sustained through Week 52 (ORR is defined as CRR or PRR). CRR was defined in primary endpoint. PRR is defined by meeting the following criteria:
      i. eGFR $\geq$ 60 mL/min/1.73m^2 or no worse than 15% below baseline.
      ii. Improvement in 24-hour UPCR:

         - For participants with a baseline UPCR $\leq$ 3.0 mg/mg: < 1.0 mg/mg
         - For participants with a baseline UPCR > 3.0 mg/mg: > 50% improvement from baseline and $\leq$ 3.0 mg/mg

         The baseline values of 24-hour UPCR and eGFR is defined in Section 4.8.1.2

      iii. No use of restricted medication beyond the protocol allowed threshold before assessment.
      iv. No discontinuation of study intervention.

   b. Response in sustained reduction of OCS dose, which is defined by meeting the following criteria:
      i. Prednisone-equivalent dose $\leq$ 2.5 mg/day by Week 24 and not exceeding this dose through Week 52.
      ii. No use of restricted medication beyond the protocol allowed threshold before assessment.
      iii. No discontinuation of study intervention.

3. Intercurrent event:

   a. Rescue medications: Captured in the variable definition.
   b. Treatment discontinuation: Captured in the variable definition.

4. Population-level summary: Difference in proportions of responders between the daxdilimab group and placebo group.

The estimand of change from baseline in eGFR at Week 52 is defined as follows, using hypothetical strategy to address intercurrent event of rescue medications by assuming data is missing as missing at random (MAR) after rescue medication and treatment policy strategy to address intercurrent event of treatment discontinuation by continue taking measures regardless of treatment discontinuation.

1. Population: Participants in the Full Analysis Set.

2. Variable (outcome measure): Change from baseline in eGFR at Week 52.

   The baseline values of eGFR are defined in Section 4.8.1.2

3. Intercurrent event:

   a. Rescue medications: The data collected after administration of the rescue medications will be treated as missing and be imputed based on assumption of MAR. That is the participants have followed the trend of his or her own treatment group
   b. Treatment discontinuation: Participants who discontinue study intervention will be asked to come to scheduled evaluations until the end of study. The data collected after discontinuation of study intervention will be included in the analysis

4. The population-level summary: Mean difference of change from baseline on eGFR between the daxdilimab group and placebo group.

4.8.2.2 Secondary Efficacy Analyses

The secondary efficacy analyses will be based on the FAS. No adjustment for multiplicity will be performed.

1) ORR will be analyzed using a logistic regression model with treatment, baseline eGFR value and baseline UPCR value included in the model. Response in sustained reduction of OCS dose will be analyzed similarly using a logistic regression model with treatment, randomization stratification factors and baseline OCS dose included in the model. The difference in proportions of responders of daxdilimab vs placebo will be estimated together with its associated 2-sided 90% confidence interval (CI).

2) Change from baseline in eGFR will be analyzed using mixed models for repeated measures (MMRM) with treatment, visit, visit by treatment interaction, randomization stratification factor (UPCR only), and baseline eGFR value included in the model. The normality test will be performed on change from baseline in eGFR. If it fails for normal assumption, the data of change from baseline in eGFR will be log-transformed. An unstructured covariance matrix will be used to model the correlations among repeated measurements within each participant. In case of convergence issues, another structure, for instance, a first-order autoregressive covariance matrix will be used. Covariance parameters will be estimated using restricted maximum likelihood method and Kenward-Roger approximation will be used to estimate denominator degrees of freedom for the tests of fixed effects. The treatment effect will be evaluated at Week 52 along with two-sided 90% CI will be reported.

3) A bar chart will be provided showing the proportion of participants meeting the criteria for ORR and individual components of ORR at [redacted] by treatment groups. A line plot up to [redacted] will also be produced by treatment groups.

4) The trajectory of eGFR over time will be visually presented by plotting the mean eGFR at each time point by treatment groups.

4.8.2.3 Supplementary Analyses of the Secondary Efficacy Endpoints

Supplementary analyses using the same models as described in section 4.8.2.2 for each secondary endpoint will be performed based on Stage I data using the full analysis set. These supplementary analyses provide additional insights for the secondary efficacy results. Treatment policy will be used to address intercurrent events of rescue medication administration and treatment discontinuation, i.e., including all observed data collected after rescue medications administration and after discontinuation of treatment.

4.8.2.4 Handling Plan for Missing Data

For ORR, the missing data will be handled in the same way as the primary efficacy analysis (section 4.8.1.7). Participants with missing outcomes due to early discontinuation from the study will be considered as non-responders. If any of the criteria cannot be evaluated at a visit, that criterion will be imputed using LOCF. For the change from baseline in eGFR, the missing data will be handled using the MMRM approach assuming MAR.

[redacted]

[redacted]

4.8.3.1.7 SDI

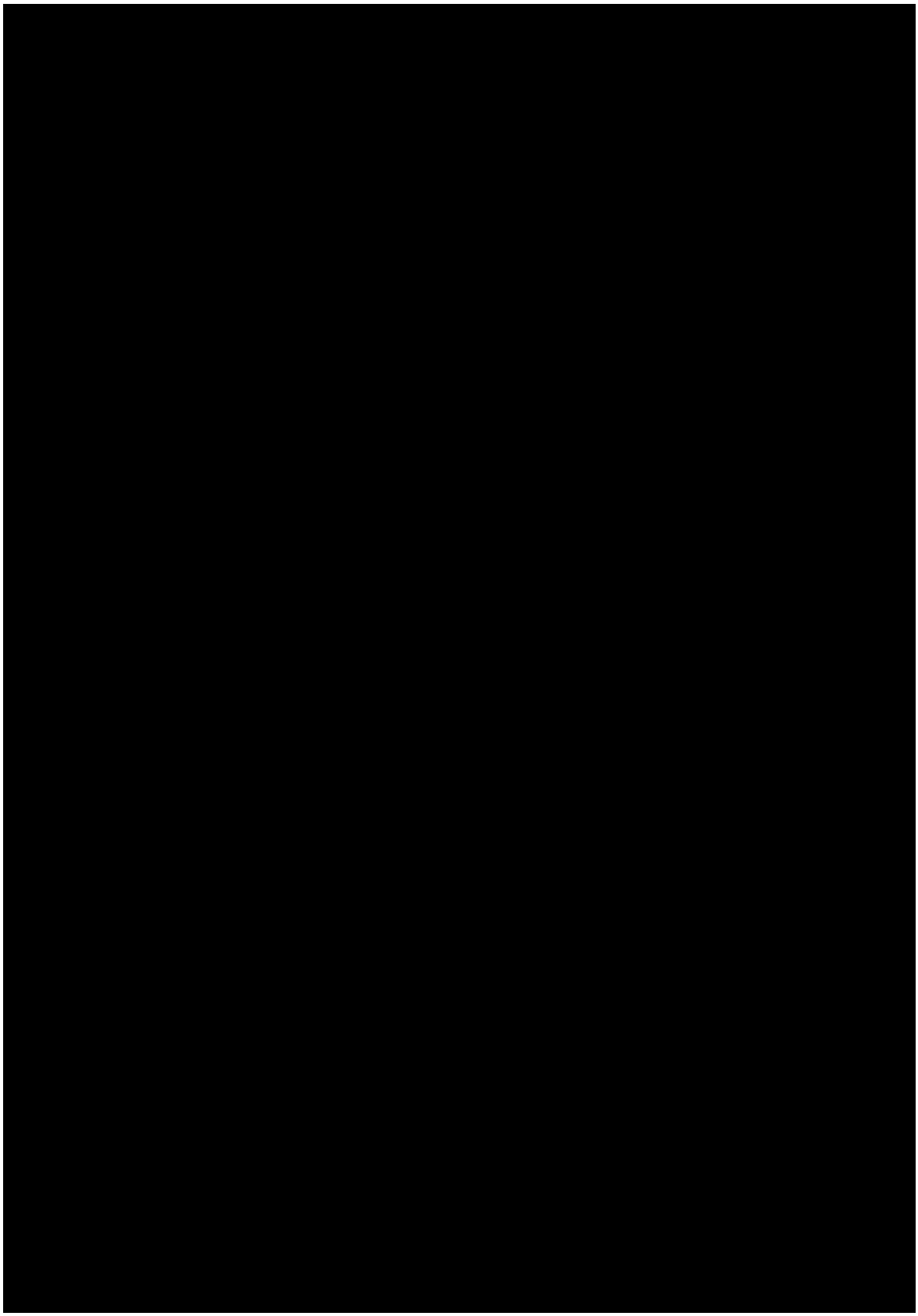
The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) has been developed to assess irreversible damage in SLE participants independently of its cause (ie, included damage due to SLE activity,

SLE-related scarring, therapy, comorbidities) but occurring after disease onset. Damage, ie, irreversible impairment since onset of SLE, is usually defined as a clinical feature that must be continuously present for at least 6 months to score. In addition, some irreversible events such as myocardial infarction or a cerebrovascular accident, score as damage on their occurrence. Briefly, damage is defined for 12 organ systems: peripheral vascular, ocular, neuropsychiatric, renal, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, skin, endocrine (diabetes), gonadal, and malignancies. Damage over time can be stable or increase, theoretically to a maximum of 47 points (Schwartz et al., 2009).

The following SLICC/ACR SDI endpoints will be explored.

- Change from baseline in SDI over time.
- Proportion of participants with any SDI worsening (change from baseline > 0) over time.

[redacted]



4.9 Safety Analyses

4.9.1 Adverse Events

Safety analyses will be based on the actual treatment received and will be performed on the Safety Analysis Set, Stage II Analysis Set or Any Daxdilimab Set according to the study period being examined. All safety data will be provided in patient listings by treatment group.

No formal hypothesis is planned. In general, if an adverse event (AE) onset is on or after the first dose of trial intervention, the AE will be considered as a treatment-emergent adverse event (TEAE). Otherwise, the AE will be considered as a non-TEAE. Safety data will be presented separately for different study periods as defined in Table 5. In addition, the total number of participants with missed doses and reasons for missing (COVID-19 related or others) will be summarized by treatment group and overall.

Table 5 TEAEs for Different Study Periods

Study Period	Inclusion of TEAEs for Summary
Stage I (Safety Analysis Set)	Include AEs with an onset on or after the first dose of trial intervention in Stage I treatment period up to the time prior to the first dose of daxdilimab in Stage II treatment period ([redacted]) for participants who were dosed during the Stage II treatment period, and AEs with an onset on or after the first dose of trial intervention in Stage I treatment for participants not dosed in Stage II treatment.
Stage II (Stage II Analysis Set)	Include AEs with an onset on or after the first dose of daxdilimab in Stage II treatment period ([redacted]).

Table 5 TEAEs for Different Study Periods

Study Period	Inclusion of TEAEs for Summary
Any Daxdilimab Exposure (Any Daxdilimab Analysis Set)	Include AEs with onset on or after the first daxdilimab dose (either during Stage I or Stage II treatment period)

All AEs and TEAEs will be coded using the most recent version of MedDRA, and will be summarized by SOC and PT overall, by severity and by relationship to treatment. Participants having multiple AEs within a category (eg, overall, SOC, PT) will be counted once in that category. Specific AEs will be counted once for each participant for calculating rates, but all events will be presented in participant listings. In addition, for severity/relationship tables, if the same AE occurs multiple times within a particular participant, the highest severity/most related event within a category and level of causality will be reported.

SAEs and TEAEs will be summarized descriptively by treatment group and overall. Percentages will be based on the number of treated participants in the safety set within a treatment group and overall. Tables will be sorted by descending frequency of SOC and by descending frequency of PT within an SOC. Specific AEs will be counted once for each participant for calculating rates, but all events will be presented in participant listings. Listings will be provided for all TEAEs and non-treatment-emergent AEs.

TESAEs will be summarized by serious adverse event (SAE) criteria as well.

The following definitions will be used for AEs:

- **Treatment-emergent adverse event (TEAE):** Any AE with an onset on or after the first dose of study intervention
- **Treatment-emergent SAE (TESAE):** A TEAE that is serious. The details are referenced in Section 8.3.1.3 of protocol

A table will show the number and percentage of participants with at least one event in any of the following categories overall as well as by SOC and PT:

- TEAE
- Treatment-emergent serious adverse event (TESAE)
- TEAE resulting in death
- CTCAE Grade 3 or higher TEAE
- TEAE leading to discontinuation of trial intervention
- Serious and/or grade 3 or higher TEAE
- Trial intervention related TEAE
- Trial intervention related TESAE

An AE of special interest (AESI) is an AE of scientific and medical interest specific to the understanding of the trial intervention and may require close monitoring and collection of additional information by the Investigator. AESIs for this protocol include:

- Hypersensitivity reaction, including anaphylaxis
- Severe viral infection/reactivation (CTCAE v5.0 Grade 3 or higher)
- Opportunistic infection as listed in protocol appendix 2
- Malignancy (except non-melanoma skin cancer)

Treatment emergent AESIs will be summarized by type of AESI as listed above as well as SOC and PT.

Anaphylaxis will be searched using the NIAID (Sampson et al. 2006). The hypersensitivity reactions will be defined using Standardized MedDRA Queries (SMQ): hypersensitivity (narrow). Severe viral infection will be searched using MedDRA HLGT of Viral infectious disorders. Viral reactivation will be searched using MedDRA HLT Hepatic viral infection. Malignancy will be searched using MedDRA SMQ Malignant tumors. All will be described in the Statistical Programming Plan (SPP).

Individual listings will be presented for AEs leading to study treatment discontinuation, AEs leading to withdrawal from the study, AEs starting during administration of study intervention, and fatal AEs.

4.9.2 Additional Safety Assessment

4.9.2.1 Clinical laboratory Evaluations

Laboratory assessments are defined in Section 8.2.4 of Protocol. All protocol-required laboratory tests must be conducted in accordance with the laboratory manual and the Schedule of Activities (SoA). Any clinically significant value will be reported as an AE. The laboratory results must be retained with source documents.

Clinical laboratory evaluations will be summarized for each treatment group and overall. The summary of clinical laboratory data will be generated for the Stage I data based on the Safety Analysis Set, and for the Stage II data based on Stage II Analysis Set. For analysis purposes, laboratory results based upon standardized units will be used. All data will be presented in listings, and a specific listing of abnormal results will be provided.

The following summary will be provided for hematology and biochemistry and lipid profile by treatment groups:

- Observed values and changes from the baseline by visit
- Worst toxicity grade
- At least 2-grade shift from baseline to worst toxicity
- Shift from the baseline relative to the normal range

In addition, the number and percentage of participants with the following liver-related abnormalities will be summarized if the following criteria is met at any post-baseline visit:

- AST or ALT: (a) $\geq 3 \times$ ULN; (b) $\geq 5 \times$ ULN; (c) $\geq 8 \times$ ULN
- Total bilirubin: $\geq 2 \times$ ULN

- ALT or AST ≥ 3 x ULN and total Bilirubin ≥ 2 × ULN
- ALT or AST ≥ 5 × ULN for more than 2 weeks

The following summary will be provided for urinalysis by treatment groups:

- Observed values and changes from the baseline by visit
- Shift from the baseline relative to the normal range

[redacted]

[redacted]

4.9.2.2 Vital Signs

The observed values, along with the changes from baseline, will be summarized at each time point by treatment for systolic blood pressure, diastolic blood pressure, body temperature, heart rate, and respiratory rate. A listing of vital signs will be presented by treatment, patient, vital sign, and visit.

In addition, a summary of participants with clinically significant vital signs values (meeting any of following criteria) will also be provided. The summary of vital signs will be generated by visit using the safety analysis set for Stage I and Stage II.

- Systolic blood pressure: < 90 mmHg, > 160 mmHg
- Diastolic blood pressure: < 60 mmHg, > 100 mmHg
- Heart rate: < 50 beats/min, > 100 beats/min
- Respiratory rate: < 12 breaths/min, > 23 breaths/min
- Temperature: < 36°C, >38°C

4.9.2.3 Prior and Concomitant Medications

Prior and concomitant medications and procedures will be summarized using the safety analysis sets accordingly. The details of prior and concomitant medications are described in Section 6.7 of the protocol.

Medications collected at Screening and during the trial will be coded using the current version of the World Health Organization Drug dictionary (WHO-DD). Number (%) of participants who received prior medications and concomitant medications will be summarized by treatment presented by WHO-DD Anatomical Therapeutic Chemical (ATC) category and PT. At each level of summarization, a participant is counted once if the participant reported one or more medications at that level. The summary of prior and concomitant medications during Stage I will be based on safety analysis set. The concomitant medications during Stage II will be summarized based on the second-year analysis set. The prior and concomitant medications are defined as below.

- Prior medications are defined as medications with a stop date occurring before the first trial intervention administration date.

- Concomitant medications during Stage I are defined as follows:
  - Medications with a start date before Week 64 trial intervention administration and stop date on or after the first trial intervention administration date for the participants entering the second-year treatment period.
  - Medications with stop date on or after the first trial intervention administration date for participants not entering the second-year treatment period.
- Concomitant medications for Stage II are defined as medications with a stop date on or after Week 64 daxdilimab administration date.

Rescue therapy for worsening LN may be administered at the discretion of Investigators as clinically indicated. Final rescue therapy will be reviewed and determined before unblinding at the end of Stage I.

Rescue therapy includes:

The initiation of any new treatment for lupus or LN with the selected restricted medications or prohibited medications as a rescue. Participants who receive rescue therapy will be considered treatment failures for subsequent endpoint analyses (such as CRR). Detailed prohibited medications are defined in the protocol Section 6.7.2, restricted medications are defined in the protocol Section 6.7.3, and rescue medicine is defined in the protocol Section 6.7.6. Additionally, certain other concomitant medications initiated after randomization beyond those allowed in protocol Section 6.7.5 may also constitute rescue therapy.

The number and percentage of participants who received rescue therapy will be summarized by treatment group according to the defined criteria using the Safety Analysis Set for Stage I and using Stage II Analysis Set for Stage II by WHO-DD ATC category and PT set.

- New Treatment

  The number and percentage of participants who received the new treatment will be summarized.

- MMF/MPA
  The number and percentage of participants who received MMF/MPA at above allowed dose by the time window will be summarized.

- Corticosteroids

  The number and percentage of participants who received corticosteroids beyond the one allowed steroid bursts, increases in corticosteroids for the prevention of adrenal insufficiency, or during the required stable dose time window from baseline will be summarized.

4.9.2.4 Electrocardiogram Results

12-lead ECGs will be performed as a safety assessment at the visits specified in Section **Error! Reference source not found.** of protocol. Any clinically significant value will be reported as an AE.

The observed values, along with the changes from baseline, will be summarized at baseline and each postbaseline time point for ventricular heart rate, PR interval, QRS duration, QT interval, and the corrected QT interval (QTc) using the safety analysis. The number (%) of participants meeting the following criteria will be summarized:

- QTc > 450 msec
- QTc > 480 msec
- QTc > 500 msec
- QTc increases from baseline > 30 msec
- QTc increases from baseline > 60 msec

Corrected QT (QTc) intervals will be derived using Fridericia's correction (QTcF) and Bazett's correction (QTcB). In addition, the overall clinical evaluation of electrocardiogram results (normal, abnormal, not clinically significant abnormal, clinically significant abnormal) will also be summarized. The summary will be produced using the Safety Analysis Set for the overall study.

4.9.2.5 Other Safety Measures

4.9.2.5.1 Overdose

The incidence of TEAEs associated with overdose will be summarized by MedDRA SOC and PT, if applicable.

4.9.2.5.2 Physical Examination and Weight

A complete physical examination will include, at a minimum, assessments of the following organs/body systems: head, ears, eyes, nose, throat, lungs, heart, abdomen, skin, and extremities. The observed values and the changes from baseline in the weight and body mass index (BMI) will be summarized. Adverse changes from baseline in physical examination findings will be classified as AEs and analyzed accordingly.

4.9.2.5.3 Local injection tolerability

The incidence of TEAEs associated with local injection tolerability will be summarized by MedDRA HLT injection site, if applicable.

4.10 Pharmacokinetic (PK) Analyses

Individual PK data will be collected for all participants. PK analyses will be performed on the PK analysis set.

Serum concentrations will be summarized descriptively by treatment and by visit with descriptive statistics including the number of observations, arithmetic mean, SD,

median, minimum, maximum, coefficient of variation, geometric mean, and geometric coefficient of variation.

Mean (±SD) serum concentration versus scheduled time profiles will be presented graphically. Actual dose administration and sampling times will be used for all calculations.

[redacted]

4.13 Immunogenicity

The ADA status will be summarized by the categories defined in Table 6. The ADA incidence rate may also be summarized by treatment group at each time point, where the incidence is the proportion of the participants with ADA positive results post-baseline only or boosted their pre-existing ADA during the study period. The cutoff for the

boosted ADA will be determined before the database lock for the primary analysis. The impact of ADA on PK will be assessed. If data allow, any confirmed ADA positive samples will be tested for ADA titer and the presence of neutralizing antibodies to daxdilimab. The number and percentage of participants who develop positive ADA will be summarized by randomized treatment group, and the impact of ADA on efficacy and safety will be evaluated.

The ADA summary will be produced for Stage I using Safety Analysis Set and for the overall study using Any Daxdilimab Analysis Set. For the overall study summary, the baseline positive is defined as any positive ADA prior to the first administration of daxdilimab.

Table 6 Definition of ADA Status

ADA Status	Definition
Prevalence (Positive during the study)	ADA positive observed at least once during the study (baseline included)
Negative during the study	ADA positive not observed at any visit during the study (baseline included)
Baseline positive	ADA positive observed at baseline regardless of the post-baseline ADA status
Post-baseline positive	ADA positive observed at least once during post-baseline regardless of the baseline ADA status
Only baseline positive	ADA positive observed at baseline but not observed at any time post-baseline
Only post-baseline positive (treatment-induced)	ADA positive not observed at baseline but observed at least once post-baseline
Both baseline and post-baseline positive	ADA positive observed at baseline and observed at least once post-baseline
Persistent positive	Treatment-induced ADA positive at ≥ 2 post-baseline assessments (with ≥ 16 weeks between first and last positive) or positive at the last post-baseline assessment
Transient positive	Treatment-induced ADA post-baseline positive but does not fulfil the criteria of persistent positive

ADA = anti-drug antibodies.

[redacted]

[redacted]

4.15 Final Analysis

The final analysis will be conducted after all participants have completed the Week 112 Visit or discontinued early from the study.

By study design, the participants may undergo the different [redacted] based upon the renal response observed at Week 48 and Week 52. Thus, in the final analysis, the participants will be divided into two subgroups based on their PRR/CRR status at the Week 48 through Week 52:

- PRR/CRR Subgroup: Participants who achieved PRR or CRR at Week 48 and sustained through Week 52 will remain in their treatment groups. Statistical modeling can be used to examine the treatment effect between treatment groups over the Stage II of treatment (i.e., [redacted] mg [redacted] vs. placebo and [redacted] mg [redacted] vs. placebo), as applicable. All endpoints defined in primary, secondary and [redacted] will be analyzed. Some key endpoints examples are highlighted below.
- Non-PRR/CRR Subgroup: Participants who did not achieve PRR or CRR at either [redacted] will be administered daxdilimab [redacted] mg SC [redacted] through [redacted] (last dose administered at [redacted]). The final analysis for this subgroup will be descriptive only. No statistical modeling will be performed and no formal statistical comparison between treatment groups will be tested. All endpoints defined in primary, secondary and [redacted] except for all time-to-event endpoints, will be analyzed. Some key endpoints examples are highlighted below.

In the final analysis, all analyses planned for the primary analysis will be rerun with the Full Analysis Set.

For the non-PRR/CRR subgroup, the following analyses up to the Week 112 visit will be covered in the final analysis using Stage II Analysis Set:

- Proportion of participate achieving PRR or CRR or [redacted] in the Stage II
- Change from baseline in eGFR. In addition, change from re-baseline (Week 64) in eGFR will be explored descriptively
- Change from baseline in UPCR. In addition, change from re-baseline (Week 64) in UPCR will be explored descriptively

- Proportion of participants with prednisone-equivalent dose ≤ 2.5 mg/day for participants with baseline OCS > 2.5 mg/day until Week 92
- [redacted]

For the PRR/CRR subgroup, the following analyses using the data up to the Week 112 visit will be covered in the final analysis using Stage II Analysis Set:

- Proportion of participate sustaining PRR or CRR or [redacted] in the Stage II
- Time to loss PRR or CRR in the Stage II after achieving PRR/CRR at Week 48 and Week 52
- eGFR slope
- Change from baseline in UPCR
- Proportion of participants with prednisone-equivalent dose ≤ 2.5 mg/day for participants with baseline OCS > 2.5 mg/day until Week 104
- [redacted]

In the final safety analysis, the data up to the Week 112 visit (see Section 4.9) will be used.

Summary statistics will be computed and displayed by treatment group for the PRR/CRR subgroup or by treatment pathway ([redacted] mg → [redacted] mg, [redacted] mg → [redacted] mg, placebo → [redacted] mg) for the non-PRR/CRR subgroup and by visit, where applicable. Descriptive statistics for continuous variables will minimally include the number of participants, mean of the observed values/change from baseline, SD, minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented. For analyses involved with statistical modeling, the analysis methods are as follow (if applicable):

- Time to loss at least PRR status: Kaplan-Meier cumulative distribution curves will be generated for each treatment group. Participants will be censored at the earliest of their treatment discontinuation time, receipt of rescue therapy, study withdrawal or death or at Week 112 when the event of at least PRR cannot sustained after Week 52. A corresponding summary table will present the number of participants at risk, the number of participants responding, and the number of participants censored at each postbaseline time point by treatment groups. The table will also present the median, along with the corresponding 2-sided 90% CI of time to response. Cox proportional hazards model will be explored (if applicable) with treatment group included in the model adjusting for eGFR and 24-hour UPCR values collected at Week 52. The hazard ratio with associated 2-sided 90% CIs and p-values will be presented
- For continuous and binary endpoint endpoints, similar analysis methods will be applied as described in Section 4.8.3.2 of the SAP
- [redacted]

[redacted]

A line plot of proportion of PRR, CRR, [redacted] over time will also be produced by randomized treatment group or treatment pathway within each of the subgroups. Boxplots of change of [redacted] will also be plotted by randomized treatment group or treatment pathway within each of the subgroups.

5 REFERENCES

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6 SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

APPENDIX 1 PREDNISONE EQUIVALENT OF ORAL GLUCOCORTICOID DOSE

Oral corticosteroids (OCS) other than prednisone may be used PO at the equivalent doses shown in Table 7.

Table 7 Prednisone Equivalent of OCS Dose

Glucocorticoid	Prednisone Equivalent Dose
PO prednisone	10 mg
Prednisolone	10 mg
Methylprednisolone	8 mg
Hydrocortisone	40 mg
Cortisone	50 mg
Triamcinolone	8 mg

PO = oral(ly); OCS = oral corticosteroids

APPENDIX 2 APPROVALS

Confirmation by the study biostatistician (or designee), biostatistics management (or designee), and the study clinical colleague or therapeutic lead (or designee) that the review of this statistical analysis plan is complete, and there is agreement on the content.

[redacted]
Associate Director, Biostatistics

Name,
Title

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I am the author of this document
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Sr Director, Biometrics

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Title

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Executive Medical Director, Clinical Development

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Title

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Source Envelope:
Document Pages: 46
Signatures: 3
Certificate Pages: 2
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Disabled
Time Zone: (UTC-06:00) Central Time (US & Canada)

Envelope Originator:
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1 Horizon Way
Deerfield, 60015
[redacted]
IP Address: [redacted]

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Status: Original
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Holder: [redacted]
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Agent Delivery Events	**Status**	**Timestamp**
Intermediary Delivery Events	**Status**	**Timestamp**
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**
Envelope Summary Events	**Status**	**Timestamps**
Envelope Sent	Hashed/Encrypted	2/2/2023 11:25:44 AM
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Signing Complete	Security Checked	2/2/2023 11:28:12 AM
Completed	Security Checked	2/2/2023 12:22:35 PM
Payment Events	**Status**	**Timestamps**