# STATISTICAL ANALYSIS PLAN

| | |
|---|---|
| **Protocol Title:** | An Open-label Extension Study to Evaluate the Long-term Safety and Tolerability of Daxdilimab (HZN-7734) in Participants with Systemic Lupus Erythematosus |
| **Name of Test Drug:** | Daxdilimab (HZN-7734) |
| **Protocol Number:** | HZNP-DAX-204 |
| **Protocol Version (Date):** | 17-Mar-2022 |
| **Analysis Type:** | All Planned Analyses |
| **Analysis Plan Version:** | v1.0 |
| **Analysis Plan Author(s):** | [redacted] |

## NOTICE OF CONFIDENTIAL AND PROPRIETARY INFORMATION

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## LIST OF TABLES

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADA | anti-drug antibodies |
| AE | adverse event |
| AESI | adverse event of special interest |
| ALT | alanine aminotransferase |
| ANA | Antinuclear antibodies |
| AST | aspartate aminotransferase |
| ATC | Anatomical Therapeutic Chemical |
| BMI | body mass index |
| CLASI | Cutaneous Lupus Erythematosus Disease Area and Severity Index |
| CLASI-A | CLASI activity |
| CLASI-D | C.LASI damage |
| ClinRO | clinician reported outcome |
| CSR | clinical trial report |
| [redacted] | |
| IP | investigational product |
| [redacted] | |
| LupusQoL | Lupus Quality of Life |
| MCP | metacarpophalangeal |
| MedDRA | Medical Dictionary for Regulatory Activities |
| [redacted] | |
| PD | pharmacodynamics |
| pDC | plasmacytoid dendritic cell |
| PGA | Physician Global Assessment |
| PGIC | Patient Global Impression of Change |
| PtGA | patient global assessment |
| PK | pharmacokinetics |
| PIP | proximal interphalangeal |
| PT | preferred term |
| PYE | Person years of exposure |
| Q1, Q3 | first quartile, third quartile |
| Q12W | once every 12 weeks |
| 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 |

| | |
|---|---|
| RECAST SLE | Phase 2 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of daxdilimab for the Treatment of Moderate to Severely Active Systemic Lupus Erythematosus |
| RF | Rheumatoid factor |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SAS | Statistical Analysis Software |
| SD | standard deviation |
| [redacted] | |
| SFU | safety follow-up |
| SLE | systemic lupus erythematosus |
| [redacted] | |
| SOC | system organ class |
| SPP | statistical programming plan |
| TEAE | treatment-emergent adverse event |
| ULN | upper limit of normal |
| VAS | visual analog scale |
| WHO-DD | World Health Organization Drug dictionary |

# SAP REVISION

| Revision Date (DD MMM YYYY) | Section | Summary of Revision | Reason for Revision |
|---|---|---|---|
| | | | |
| | | | |

# 1 INTRODUCTION

This document describes the statistical analysis for protocol HZNP-DAX-204, an open-label extension study to evaluate the long-term safety and tolerability of daxdilimab (HZN-7734) in participants with systemic lupus erythematosus (SLE).

# 2 TRIAL OVERVIEW

## 2.1 Trial Objectives and Endpoints

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

**Table 1 Primary, Secondary, and Exploratory Objectives**

| Objectives | Endpoints |
|---|---|
| Primary Objective | |
| To evaluate the long-term safety and tolerability of 200 mg Q12W daxdilimab | Incidence of AEs, SAEs, and AESIs |
| Secondary Objectives | |
| To characterize the PK, PD, and immunogenicity of daxdilimab | Daxdilimab concentrations, change in pDCs, and ADA rate |
| Exploratory Objectives | |
| [redacted] | |

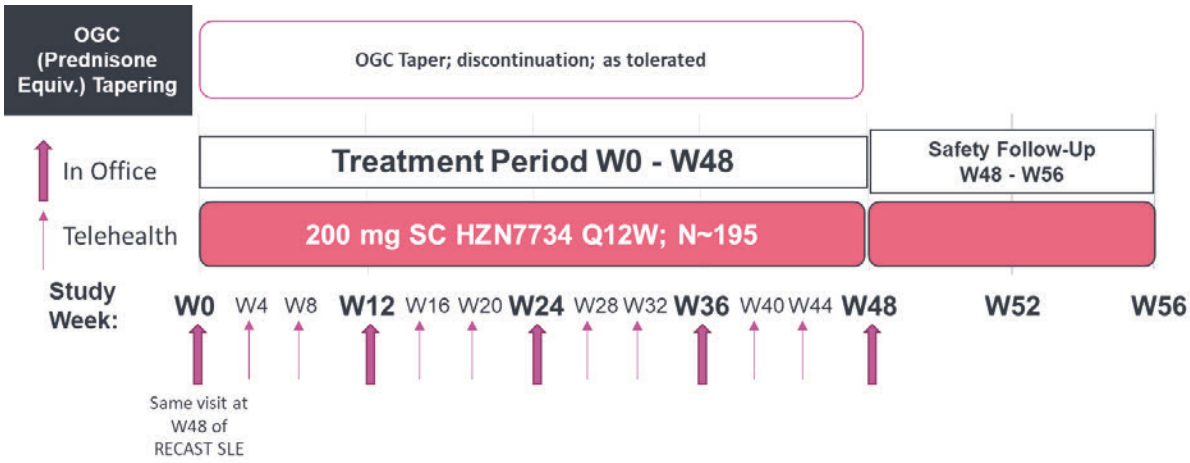
ADA = anti-drug antibodies; AE = adverse event; AESI = AE of special interest; [redacted] PD = pharmacodynamic(s); pDC = plasmacytoid dendritic cell; PGA = Physician Global Assessment; PK, pharmacokinetic(s); Q12W = every 12 weeks; RECAST SLE = Phase 2 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of daxdilimab for the Treatment of Moderate to Severely Active Systemic Lupus Erythematosus; [redacted] SAE = serious AE; SLE = systemic lupus erythematosus; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000.

## 2.2 Trial Design

This is an open-label study designed to evaluate the long-term safety and tolerability of daxdilimab in participants completing the treatment period of the VIB7734.P2.S1 (RECAST SLE) clinical study. Once a participant has completed the treatment period (through Week 48) of the RECAST SLE study, signed the informed consent form, and met all study

eligibility criteria, he/she may be enrolled in this open label extension (OLE) study. Irrespective of their assigned treatment in the RECAST SLE study, all participants participating in the SLE OLE will be treated with daxdilimab 200 mg SC Q12W in addition to their standard-of-care SLE therapy for 48 weeks. After the treatment period (Week 0 to Week 48), the participants will enter an 8-week safety follow-up (SFU) period (Week 48 to Week 56). The basic study flow diagram is presented in Figure 1. Refer to Protocol for detailed trial design.

Figure 1 Study Flow Diagram




## 2.3 Sample Size Determination

Sample size determination is based on the number of participants who have completed the treatment period of Study VIB7734.P2.S1 (RECAST SLE). A total of 195 participants have been randomized in the RECAST SLE study. Assuming that 20% of participants will prematurely discontinue treatment, there will be a total of approximately 156 participants who will be eligible for this long-term safety study.

# 3 PLANNED ANALYSES

## 3.1 Final Analysis

The final analysis will be performed when all participants have completed trial.

# 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. Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of participants in each category will be presented; for continuous variables, the number of participants (n), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

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

### 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 investigational product (IP) in Study RECAST SLE. In cases where baseline measurements are taken on the same day as IP and no times are reported, it will be assumed that these measurements are taken prior to IP being administered.

For immunogenicity analyses, baseline is defined as the last non-missing valid observation prior to the first dose of daxdilimab (either in OLE or RECAST SLE study).

### 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 biomarker data analyses 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 visits of the RECAST SLE study and OLE study, and the Week 48 visit. The detailed analysis visit windows will be specified in SPP.

The actual assessment day will be mapped to the windows defined for each scheduled study visit with 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.

All observations will be included in data listings.

### 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 major and minor prior to the database lock. The number and percentage of participants with major protocol deviations by deviation reason (eg, nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized. A by-participant listing will be provided for all protocol deviations.

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 Primary Hypothesis

No formal statistical hypothesis will be evaluated.

## 4.4 Analysis Sets

### 4.4.1 OLE Safety Analysis Set

The OLE safety analysis set is defined as participants who received any dose of daxdilimab in this OLE study. The OLE safety analysis set will be used for the safety and pharmacodynamics (PD) analyses.

### 4.4.2 Full Analysis Set

The full analysis set is defined as participants who were randomized and received any dose of IP in study RECAST SLE. Participants will be analyzed according to the treatment to which they were randomized in RECAST SLE study. The exploratory efficacy analyses will be based on the full analysis set.

### 4.4.3 Any Daxdilimab Analysis Set

The any daxdilimab analysis set includes all participants who receive at least one dose of daxdilimab in study RECAST SLE or this OLE study. The any daxdilimab analysis set will be used for the adverse events and immunogenicity analyses.

### 4.4.4 Pharmacokinetic Analysis Set

The PK analysis set is defined as participants who received any dose of daxdilimab in this OLE study and have at least one measurable PK concentration post dose. The PK analyses will be based on PK analysis set.

## 4.5 Participant Disposition

A summary of participant disposition will be presented for the full analysis set using the categories presented below.

- Completed Week 48 in RECAST SLE
- Enrolled in OLE
- Enrolled but not treated
- Enrolled and treated
- Completed treatment
- Discontinued treatment with reasons
- Completed trial
- Discontinued trial with reasons

## 4.6 Investigational Product Exposure

The number of doses received, amount of daxdilimab received, durations of daxdilimab exposure, and total person years of exposure will be summarized for this OLE study using OLE safety analysis set, and together with Study RECAST SLE using the full analysis set, respectively. The number and percentage of participants treated ≥12 weeks, ≥ 24 weeks, ≥ 36 weeks, and ≥ 48 weeks will also be provided.

- Durations of daxdilimab exposure is defined as:
  - OLE study: last dose date in OLE study + 28 – first dose date in OLE study + 1;
  - Any daxdilimab exposure: last dose date in OLE study + 28 – first daxdilimab dose date in study RECASE SLE or study OLE + 1.
- Person years of exposure (PYE) = durations of exposure / 365.25.
- The amount of study daxdilimab exposure: if a participant received partial dose at a dosing visit, then the amount of daxdilimab at that dosing visit will be estimated based on the actual volume administered.

## 4.7 Demographics, Baseline Characteristics, and Medical History

The demographics (age, gender, race, ethnicity, height, weight, and body mass index), and baseline characteristics from study RECAST SLE will be summarized. Table 2 provides the list of baseline characteristics to be summarized using the OLE safety analysis set.

**Table 2 Baseline Characteristics**

- Time from initial diagnosis to randomization
- [redacted]
- Physician global assessment (PGA) score
- Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity (CLASI-A) and damage (CLASI-D) score
- [redacted]
- Antinuclear antibodies (ANA) (positive, negative)
- [redacted]
- Rheumatoid factor (RF) (positive/negative)
- Region (Europe, North America, Latin America, and Asia)

Significant medical history finding from the RECAST SLE study will be summarized by MedDRA system organ class (SOC) and preferred term (PT) for the OLE safety analysis set.

## 4.8 Exploratory Efficacy Analyses

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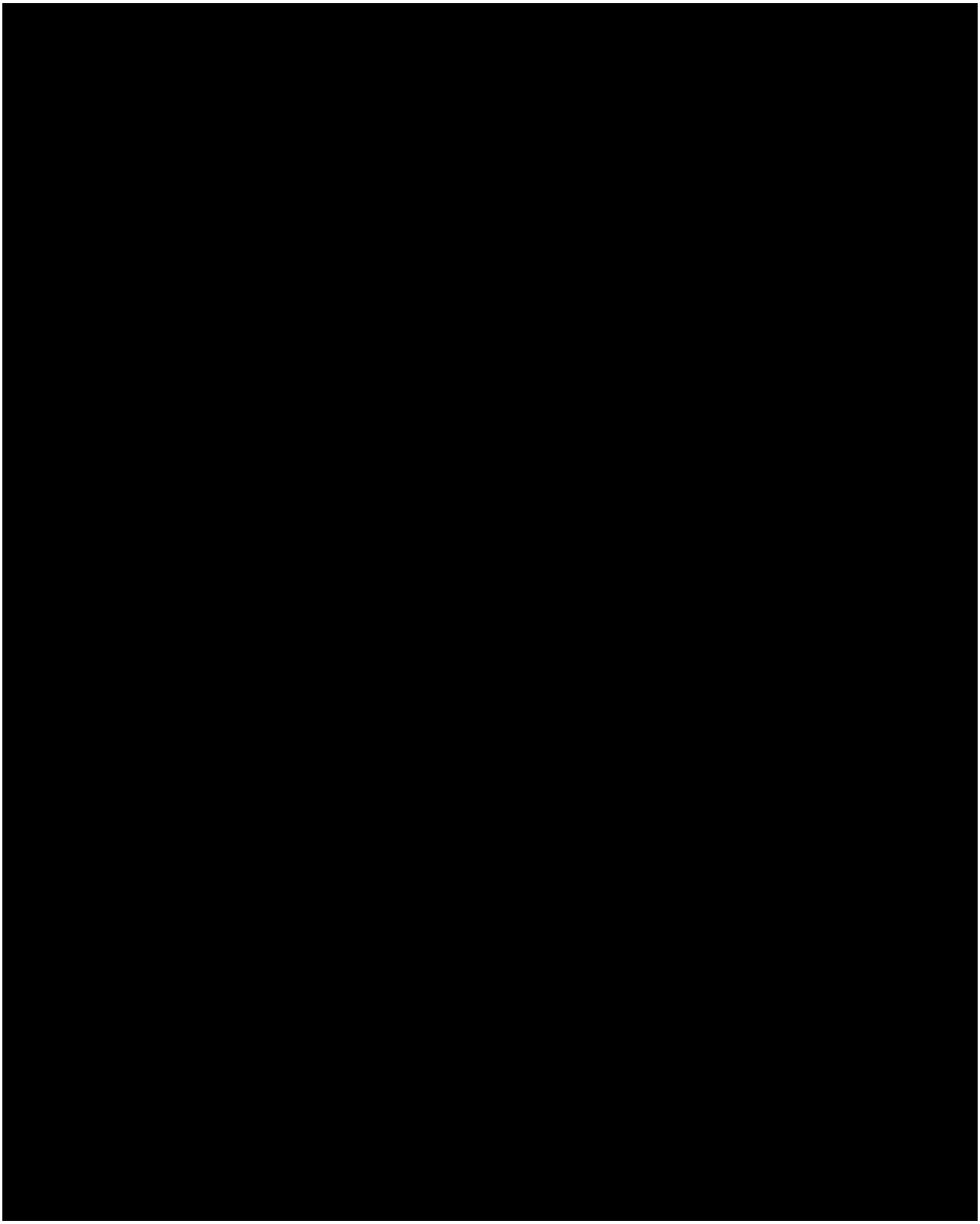

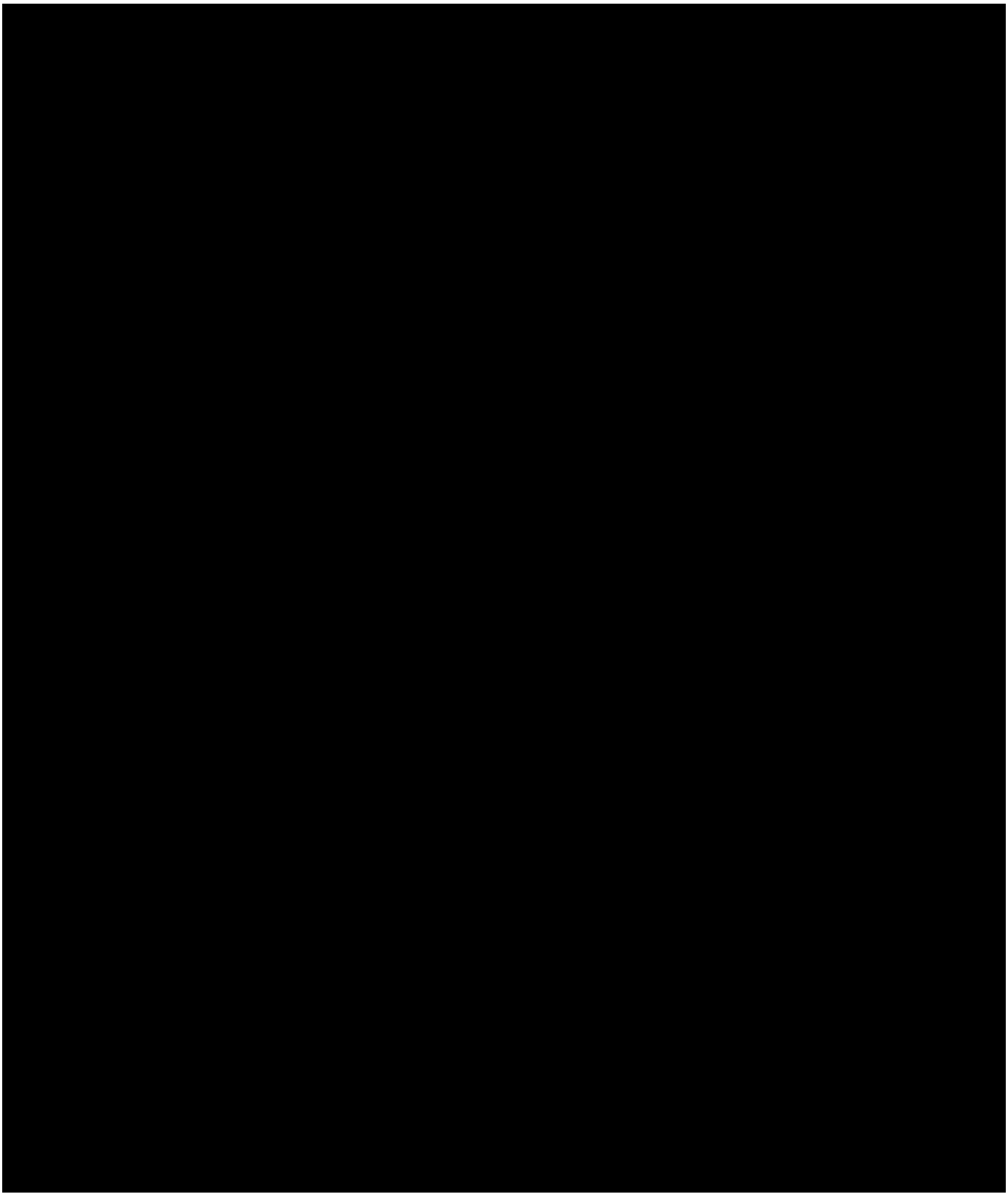

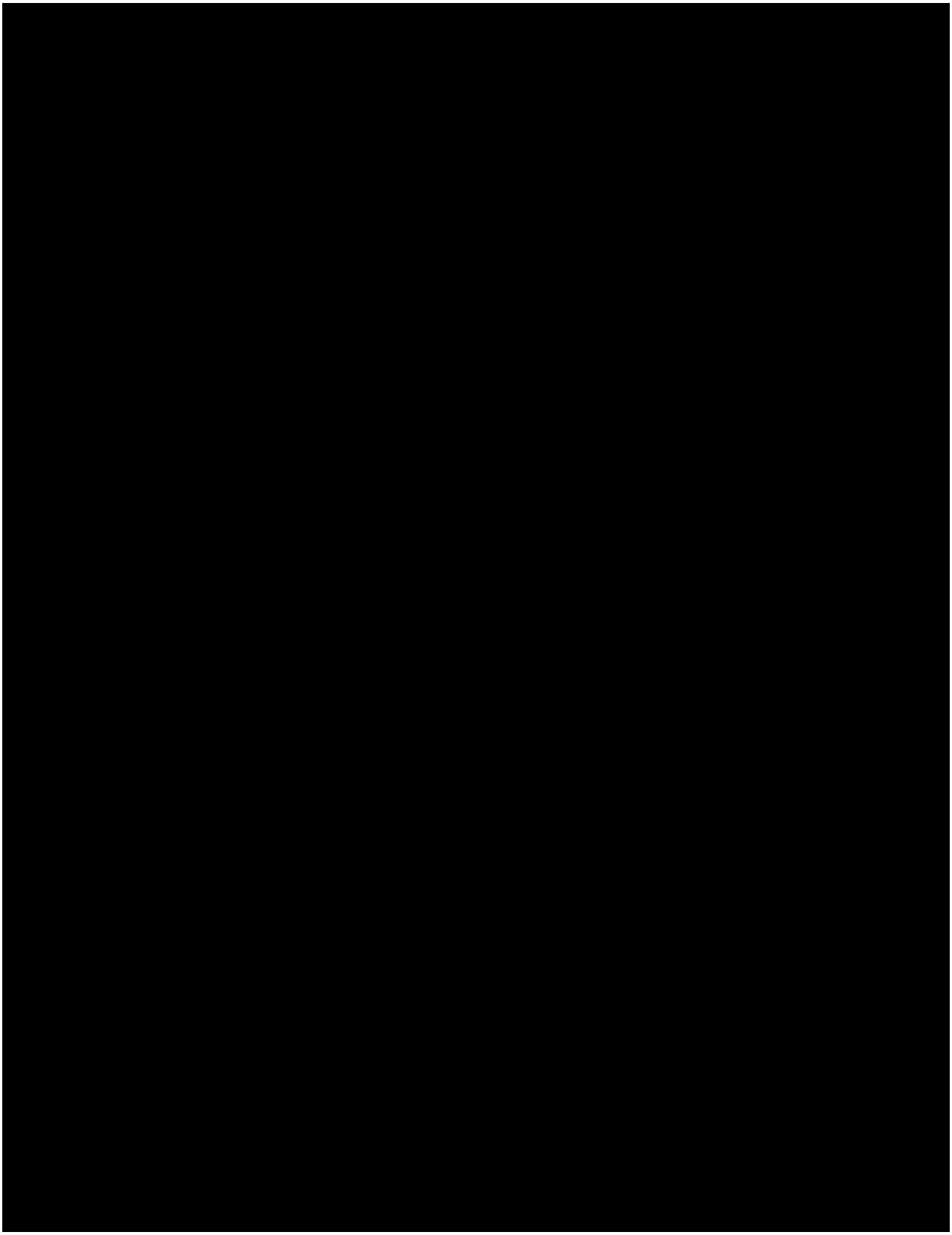

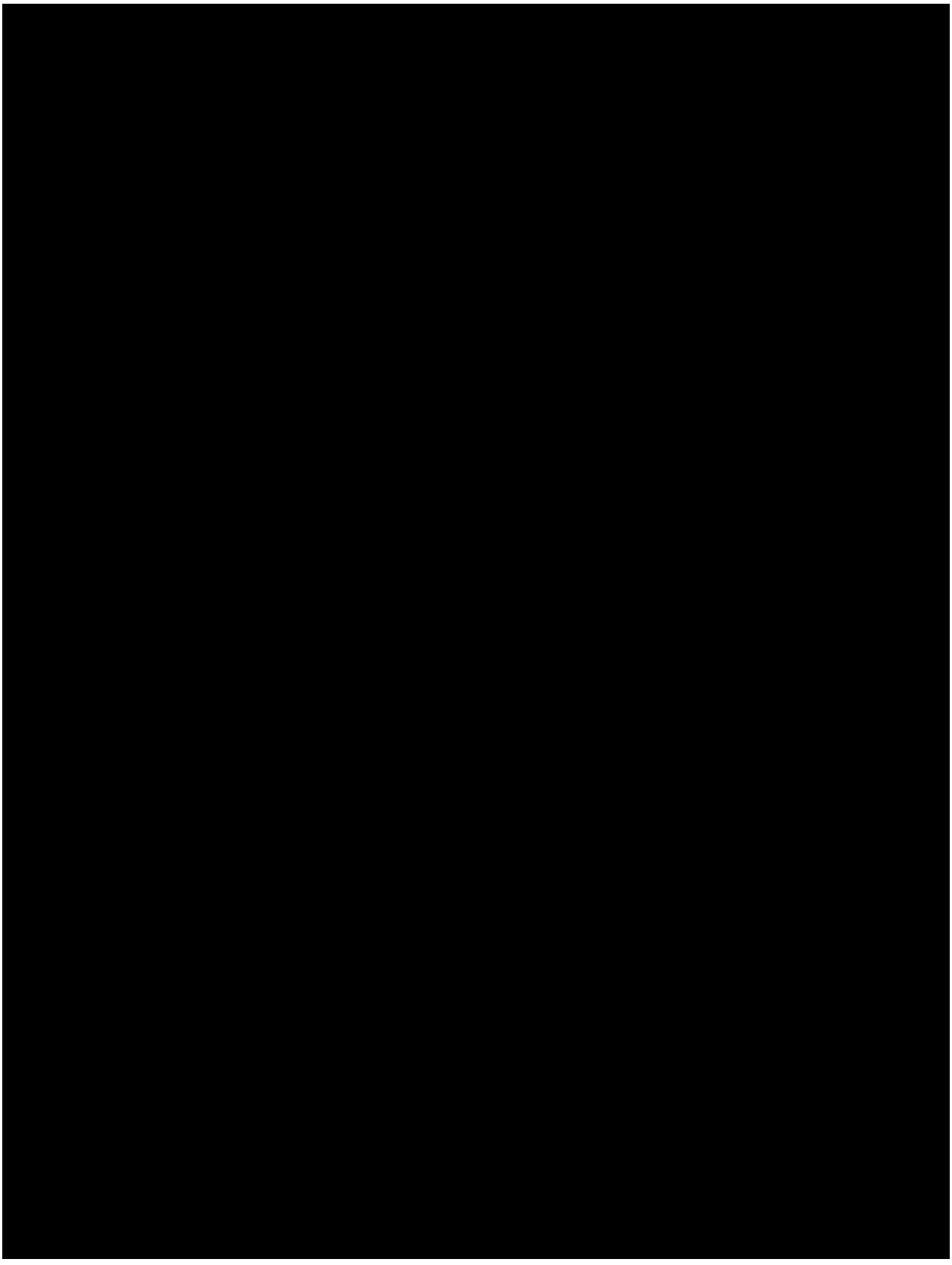

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## 4.9 Safety Analyses

### 4.9.1 Adverse Events

Adverse events (AEs) collected in this OLE study will be summarized separately using the OLE safety analysis set and together with the AEs collected in study RECAST SLE using the any daxdilimab analysis set overall and by treatment group. Table 4 presents the definition of treatment-emergent adverse event (TEAE) for reporting purposes.

**Table 4 Definition of TEAEs**

| Study | Definition |
|---|---|
| OLE | A TEAE is defined as any AE with an onset date on or after the first dose date in the OLE study. |

**Table 4 Definition of TEAEs**

| Study | Definition |
|---|---|
| OLE + RECAST SLE (Any daxdilimab exposure) | A TEAE is defined as any AE with an onset date on or after the first daxdilimab dose date (either in OLE or RECAST SLE study) |

AEs will be coded using the most recent version of MedDRA. All TEAEs will be summarized overall and by MedDRA system organ class (SOC) and preferred term (PT), by severity and by relationship to daxdilimab. Specific AEs will be counted once for each participant for calculating rates, but all events will be presented in participant listings. In addition, if the same AE occurs multiple times within a particular participant, the highest severity and level of causality will be reported.

In addition, since the duration of exposure to daxdilimab is shorter for the participants who received placebo in the RECAST SLE study, the PYE adjusted incidence rate for the number of participants who experienced TEAE will be included in the combined summary of OLE + RECAST SLE using any daxdilimab analysis set. Refer to Section 4.6 for definition of PYE.

An overall summary table will be showing the number and percentage of participants with at least one event in any of the following categories:

- TEAE
- Treatment-emergent serious adverse event (TESAE)
- TEAE resulting in death
- Grade 3 or higher TEAE using CTCAE v5.0
- TEAE leading to discontinuation of daxdilimab
- Serious and/or grade 3 or higher TEAE
- Daxdilimab related TEAE
- Daxdilimab related TESAE

The following AE summaries will also be provided by SOC and PT:

- TEAEs
- TEAEs resulting in death
- Grade 3 or higher TEAEs using CTCAE v5.0
- TEAE leading to discontinuation of daxdilimab
- Daxdilimab related TEAE
- TESAEs
- Daxdilimab related TESAE

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

- Hypersensitivity reaction, including anaphylaxis
- Severe (Grade 3 or higher) viral infections/reactivations

- Opportunistic infection as listed in the Appendix 6 of the protocol (all cases)
- Malignancy (except non-melanoma skin cancer)

Treatment emergent AESIs will be summarized by SOC and PT. TESAEs will be summarized by serious adverse event (SAE) criteria as well. A summary of TEAEs sorted by frequency will be presented by PT.

Listings will be provided for all TEAEs and non-treatment emergent AEs collected in this OLE study and RECAST SLE.

### 4.9.2 Clinical Laboratory Evaluations

The following summary will be provided for hematology, coagulation, chemistry, and lipid profile parameter for the OLE safety analysis set using the OLE data.

- Observed values and changes from the baseline by visit
- Worst toxicity grade
- ≥ grade 3 toxicity post-baseline
- Shift from the baseline relative to the normal range
- Shift from baseline to worst toxicity grade

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

- AST or ALT: (a) ≥ 3 × ULN; (b) ≥ 5 × ULN; (c) ≥ 8 × ULN
- Total bilirubin: ≥ 2 × 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.

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

Observed values and changes from baseline will be summarized descriptively for high-sensitivity C-reactive protein (hs-CRP) and immunoglobulins parameters.

Listings will be provided for all clinical laboratory evaluations collected in this OLE study.

### 4.9.3 Vital Signs

The observed values, along with the changes from baseline, will be summarized for systolic blood pressure, diastolic blood pressure, body temperature, heart rate, and respiratory rate using the OLE safety analysis set based on OLE data. In addition, a summary of participants with clinically significant vital signs values (meeting any of following criteria) will also be provided.

- 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

### 4.9.4 Concomitant Medications

Medications collected during the trial will be coded using the current version of the World Health Organization Drug dictionary (WHO-DD). Number (%) of participants who received medications in this OLE study will be summarized by WHO-DD Anatomical Therapeutic Chemical (ATC) category and PT for the OLE safety analysis set. At each level of summarization, a participant is counted once if the participant reported one or more medications at that level.

The number and percentage of participants who receive rescue medications will be summarized. Rescue medications are:

- Any new permitted treatment to improve SLE disease activity, or
- An increase from Day 1 dose in this study in therapies, such as antimalarials, methotrexate, mycophenolate mofetil/mycophenolic acid, corticosteroid, or azathioprine.

The detailed rescue medications will be identified and finalized by medical monitor before database lock. The missing start/stop date will be imputed as appropriate, and the details of the imputation will be included in the SPP.

### 4.9.5 Electrocardiogram Results

The observed values, along with the changes from baseline, will be summarized for ventricular heart rate, PR interval, QRS duration, QT interval, and the corrected QT interval (QTc) using the OLE safety analysis set based on OLE data. 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. Listings will be provided for all electrocardiograms results collected in this OLE study.

### 4.9.6 Other Safety Measures

#### 4.9.6.1 Overdose

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

#### 4.9.6.2 Physical Examination and Weight

The observed values and the changes from baseline in the weight and body mass index (BMI) will be summarized using the OLE safety analysis set based on OLE data.

#### 4.9.6.3 Local injection tolerability

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

## 4.10 Pharmacokinetic (PK) Analyses

The PK analysis will be based on the PK analysis set. Descriptive statistics of the serum daxdilimab concentration will be tabulated by visit.

Additional PK analyses may be conducted as appropriate and reported separately from the clinical study report.

## 4.11 Pharmacodynamics

The observed count along with the change and percent change from baseline in pDCs will be summarized descriptively using the OLE safety analysis set based on OLE data.

## 4.12 Immunogenicity

The ADA status will be summarized using the any daxdilimab analysis set by the categories defined in Table 5. The ADA incidence rate may also be summarized, where the incidence is the proportion of the participants with ADA positive 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. If data allow, the ADA titer for the ADA positive participants will be summarized, and the impact of ADA on PK, efficacy and safety will be evaluated.

**Table 5 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 the post-baseline ADA status |

**Table 5 Definition of ADA Status**

| ADA Status | Definition |
|---|---|
| Post-baseline positive | ADA positive observed at least once during post-baseline regardless 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 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.

# 5 SOFTWARE

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

## APPENDIX 1 PREDNISONE EQUIVALENT OF ORAL GLUCOCORTICOID DOSE

Oral GCs other than prednisone may be used PO at the equivalent doses shown in **Error! Reference source not found.**.

# 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.

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[redacted]
Signer Name: [redacted]
Signing Reason: I am the author of this document
Signing Time: 03-Jun-2022 | 10:04 CDT
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[redacted]
Sr Manager, Biostatistics

03-Jun-2022 | 10:04 CDT

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Title

Signature/Date

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Sr Director, Biometrics

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Sr Medical Director, Clinical Development

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