Janssen Research & Development

Statistical Analysis Plan
Amendment 1

A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study of Guselkumab in Participants with Active Lupus Nephritis

Protocol CNTO1959LUN2001; Phase 2

CNTO1959 (Guselkumab)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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VERSION HISTORY

SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1.0	13 August 2020	Not Applicable	Initial release, draft approved for dossier use
2.0	16 August 2022	**All sections:** Added and/or modified text at the beginning of sections and subsections to clarify changes in the statistical analysis plan due to early study termination, and to clarify the analyses that will be included in the CSR.	Statistical analysis plan is changed due to early termination of the study
		Section 1.2: Minor updates on study design per protocol; **Section 5.1:** Removed baseline definition for proteinuria as the general baseline definition will be used; **Section 5.2:** Updated the timepoint for disposition summary; **Section 5.4.2.2.7.1:** Updated ICEs for the main estimand for time to achievement of CRR; **Section 5.4.2.3:** Updated analysis method for Secondary Endpoint 2. **Section 5.5.1**: Minor updates on definition of endpoints for clarity; **Section 5.6:** Minor updates in analysis methods. **Section 5.7**: Minor edits for clarity.	Minor updates for clarification

1. INTRODUCTION

This Statistical Analysis Plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for all planned analyses of efficacy, safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity of guselkumab. This SAP incorporates all analyses through the final database lock (DBL) for the CNTO1959LUN2001 study.

Early Termination Note: The original study design included a target of approximately 60 participants to be randomly assigned with approximately 30 participants planned per intervention group. Due to the Sponsor's decision to stop screening of new participants as a result of enrollment challenges, fewer than 60 participants will be enrolled in the study. The end of study will occur after all enrolled participants have completed the Week 20 visit or discontinued study intervention prior to Week 24, and all participants have completed their final efficacy and safety visits per the Schedule of Activities (SoA).

There will be only one database lock that will occur at the end the study. All data through the end of the study including the long term extension (LTE) data will be summarized together. Analyses that will be performed and included in the abbreviated Clinical Study Report (CSR) are noted below at the beginning of each respective section. The analyses not performed will be retained in this SAP for completeness.

1.1. Objectives and Endpoints

Due to the Sponsor's decision to terminate the study early, only the primary endpoint, major secondary endpoints, and safety endpoints will be reported in the CSR. Details will be described in each respective section.

For informational purposes, the below table outlines the objectives and endpoints originally planned for the study.

Objectives	Endpoints
Primary	
• To evaluate the efficacy of guselkumab in participants with active lupus nephritis (LN)	**Primary endpoint**: Proportion of participants achieving at least 50% decrease in proteinuria from baseline at Week 24 **Secondary endpoints** to include: • Proportion of participants achieving complete renal response (CRR) at Week 24 • Proportion of participants achieving a sustained reduction in steroid dose ≤10 mg/day of prednisone or equivalent from Week 16 to Week 24 • Proportion of participants achieving at least 50% decrease in proteinuria from baseline at Week 52 • Proportion of participants achieving CRR at Week 52 • Proportion of participants with Urine Protein to Creatinine Ratio (UPCR) <0.5 mg/mg at Week 24

Objectives	Endpoints
	• Proportion of participants with UPCR <0.75 mg/mg at Week 24 • Time to achievement of CRR • Time to treatment failure (TF)
Secondary	
• To evaluate the safety and tolerability of guselkumab in participants with active LN	• Frequency and type of adverse events (AEs), serious adverse events (SAEs), reasonably related AEs, AEs leading to discontinuation of study intervention, infections, serious infections, and infections requiring oral or parenteral antimicrobial treatment, AEs temporally associated with an infusion, and injection-site reactions • Laboratory parameters and change from baseline in laboratory parameters (hematology and chemistry) • Summary of maximum Common Terminology Criteria for Adverse Events (CTCAE) toxicity grade for postbaseline laboratory values (hematology and chemistry) • Systolic and diastolic blood pressures over time
• To evaluate the PK, immunogenicity, in participants with active LN	• Serum guselkumab levels over time • Serum anti-guselkumab antibodies through Week 24, through Week 52, and in participants discontinuing study intervention early
Tertiary/Exploratory	
• To evaluate the efficacy of guselkumab in extrarenal lupus manifestations	• Proportion of participants with ≥4-point improvement at Week 24 in systemic lupus erythematosus disease activity index 2000 (SLEDAI-2K) modified to exclude renal items • Proportion of participants with baseline arthritis (with at least 4 active joints at baseline) who have ≥50% reduction in active joints at Week 24 • Proportion of participants with baseline active mucocutaneous lupus manifestations (CLASI score ≥8) and ≥50% reduction in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) scores at Week 24
• To evaluate the impact of guselkumab on Health-Related Quality of Life (HRQoL) and fatigue in participants with active LN	• Change from baseline in Lupus Quality of Life (LupusQoL) individual domains at Week 24 • Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue score at Week 24 • Change from baseline in lupus symptoms (joint pain, joint stiffness, rash, and swelling [peripheral edema]) at Week 24 • Patient Global Impression of Change (PGIC) - Change in LN (health condition) at Week 24 and Week 52

Objectives	Endpoints
• To evaluate biomarkers of LN, pharmacodynamic (PD) effects of guselkumab, and to identify participants most likely to benefit from treatment with guselkumab	• Serum biomarkers including IL-23, IL-17A, IL-17F, IL-22, complement (C)3, C4, C1q, or autoantibodies, eg, anti-dsDNA • Cellular (urine and peripheral blood mononuclear cell [PBMC]) and whole blood gene expression • Urine biomarkers (protein and /or nucleic acids)
• Perform analyses of pre- and post-treatment renal biopsies (optional)	• Histopathology of glomeruli and tubulointerstitial tissue, immunohistochemistry for resident and infiltrating cell types and inflammatory mediators (including IL-23, IL-17, IL-21, interferon-gamma, chemokines), and/or tissue gene expression

1.2. Study Design

Early Termination Note: Due to the Sponsor's decision to stop screening of new participants as a result of enrollment challenges, fewer than 60 participants will be enrolled in the study. The end of study will occur after all enrolled participants have completed the Week 20 visit or discontinued study intervention prior to Week 24, and all participants have completed their final efficacy and safety visits per the SoA.

CNTO1959LUN2001 is a randomized, double-blind, placebo-controlled, parallel, multicenter, interventional Phase 2 study in participants aged 18 to 75 (inclusive) with active lupus nephritis (LN). The total duration of the study is up to 68 weeks: a ≤8-week screening period (rescreening is permitted once per participant), a 48-week double-blind treatment period, and a 12-week safety follow-up period after the last dose (8 weeks after the final efficacy visit). Participants starting mycophenolate mofetil (MMF) / mycophenolic acid (MPA) at/or within 2 weeks of screening may extend screening for up to 2 additional weeks.

Efficacy, safety, PK, immunogenicity, and biomarkers (where local regulations permit) will be assessed according to the SoA in the study protocol. An optional pharmacogenomic blood sample will be collected from participants who consent to the collection of these samples (where local regulations permit).

The primary efficacy analysis will be performed after all participants have completed Week 24 efficacy assessments (or discontinued). Additional secondary endpoints will be completed at Week 24 and Week 52.

Every reasonable effort should be made to keep concomitant medications stable as defined in the protocol. Beginning at the screening visit, all concomitant therapies and all changes in concomitant therapies should be recorded throughout the study.

Key safety assessments include AEs, clinical laboratory tests (hematology and chemistry), systolic and diastolic blood pressures over time, monitoring for hypersensitivity reactions, AEs temporally

associated with infusion, injection-site reactions, suicidality assessment, and early detection of active tuberculosis.

Participants who complete the Week 52 visit and achieve a CRR, may have the option to participate in a LTE study.

Due to study termination, only one DBL will occur at the end of study.

An external, independent Data Monitoring Committee (DMC) will be commissioned for this study. The DMC will review unblinded data on a periodic basis to ensure the safety of participants enrolled in the study. The main focus of the DMC will be on reviewing interim unblinded safety data, but the DMC may also review efficacy data needed to ensure the full benefit:risk profile for guselkumab. The DMC responsibilities, authorities, and procedures will be documented in a separate DMC charter.

NUMBER OF PARTICIPANTS

A target of approximately 60 participants will be randomly assigned in a 1:1 ratio to study intervention in this study, with approximately 30 participants planned per intervention group.

INTERVENTION GROUPS AND DURATION

Participants in the study will maintain their standard-of-care treatment of mycophenolate mofetil (MMF)/mycophenolic acid (MPA) and background glucocorticoid. Participants' glucocorticoid dose will be tapered.

Participants will be randomized to 1 of 2 intervention groups in a 1:1 ratio as described below:

- Guselkumab: Participants will receive guselkumab 400 mg intravenously (IV) at Weeks 0, 4 and 8 (ie, 3 IV doses) and guselkumab 200 mg subcutaneous (SC) every 4 weeks (q4w) from Week 12 through Week 48.
- Placebo: Participants will receive placebo IV at Weeks 0, 4 and 8 (ie, 3 IV doses) and placebo SC q4w from Week 12 through Week 48.

Participants will be stratified by geographic region (North America, Latin America, Asia Pacific and Europe) and Urine Protein to Creatinine Ratio (UPCR) level (<3 mg/mg and ≥3 mg/mg).

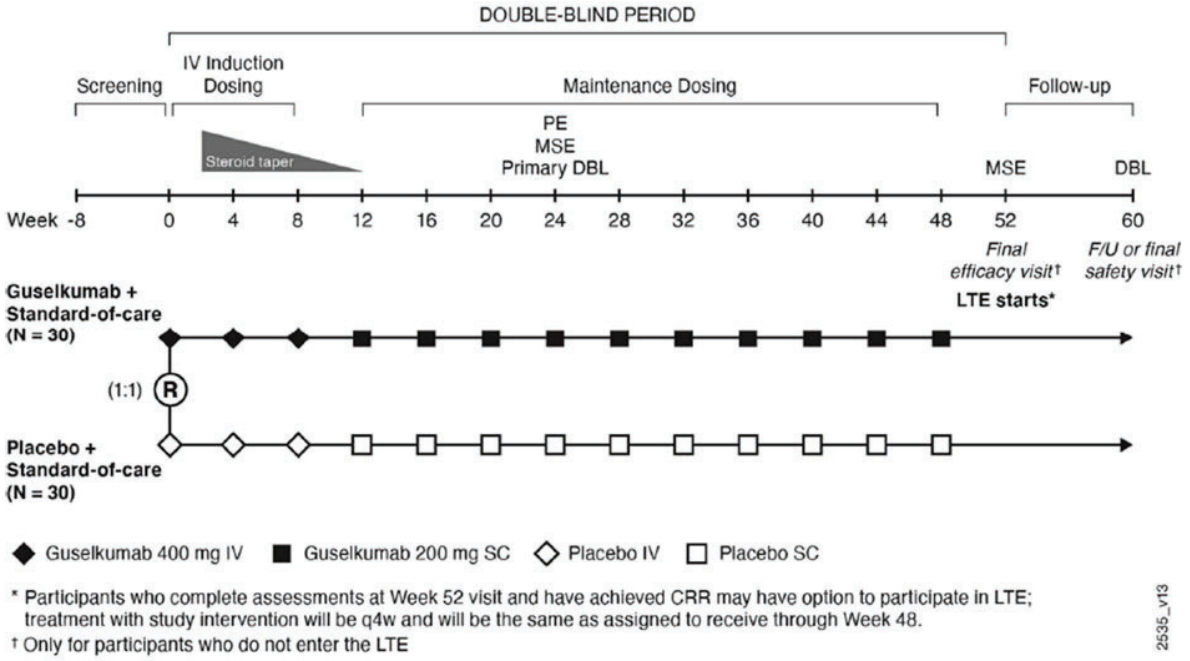
Participants will remain on their assigned treatment through Week 48. All participants will receive an IV infusion (either active or placebo) at Weeks 0, 4, and 8 and 2 SC injections (either active or placebo) at Week 12 then q4w through Week 48.

Eligible participants will continue to receive the same study intervention q4w (placebo or guselkumab) in the LTE. The first dose in the LTE will be at Week 52.

The study participants will remain blinded throughout the study (including the LTE). Due to study termination, one DBL for the study will occur at the end of study. The end of study will occur after all enrolled participants have completed the Week 20 visit or discontinued study intervention prior to Week 24, and all participants have completed their final efficacy and safety visits per the SoA.

The study schema is provided in Figure 1.

Figure 1: Schematic Overview of the Study



Abbreviations: CRR=complete renal response; DBL=database lock; F/U=follow-up; LTE=long-term extension; IV=intravenous; MSE=major secondary endpoint; N=number of participants; PE=primary endpoint, R=randomization; SC=subcutaneous; SOC=standard-of-care.

2. STATISTICAL HYPOTHESES

The primary hypothesis of this study is that guselkumab plus standard-of-care is superior to placebo plus standard-of-care in participants with active LN as measured by the proportion of participants inducing at least a 50% reduction of proteinuria with protocol specified steroid tapering regimen at Week 24.

3. SAMPLE SIZE DETERMINATION

Early Termination Note: Due to the Sponsor's decision to stop screening of new participants as a result of enrollment challenges, fewer than 60 participants will be enrolled in the study. The end of study will occur after all enrolled participants have completed the Week 20 visit or discontinued study intervention prior to Week 24, and all participants have completed their final efficacy and safety visits per the SoA.

The sample size section below is the originally planned sample size.

Approximately 60 participants are planned to be randomized into the study.

The study will be considered a success if the 1-sided p-value for testing the difference in proportion of participants with ≥50% decrease in proteinuria between the guselkumab and placebo

intervention groups based on a logistic mixed effect repeat measurement longitudinal model is less than a 1-sided alpha level of 10%.

Table 1 shows the sensitivity, with respect to various assumed between group difference, of estimated power to detect a difference in proportions of participants with ≥50% decrease in proteinuria between the guselkumab and placebo intervention groups at Week 24.

Table 1: Power to Detect Difference in Proportions of Participants with ≥50% Decrease in Proteinuria Between the Guselkumab and Placebo Intervention Groups at Week 24

Difference in proportion of participants with ≥50% decrease in proteinuria between the intervention groups	Power (%)
20%	56.34
25%	79.61
30%	89.84
35%	96.08

Notes:
- Proportion of placebo participants with ≥50% decrease in proteinuria is assumed to be 49%.
- Power calculation is based on 1-sided α of 0.10.
- Total sample size is 60.

If the proportion of placebo participants with ≥50% decrease in proteinuria is 49%, and the difference in proportion between the intervention groups is 30%, a total sample size of 60 with a 1-sided alpha of 10% will provide approximately 90% power for success.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Early Termination Note: Due to the Sponsor's decision to stop screening of new participants as a result of enrollment challenges, fewer than 60 participants will be enrolled in the study. The end of study will occur after all enrolled participants have completed the Week 20 visit or discontinued study intervention prior to Week 24, and all participants have completed their final efficacy and safety visits per the SoA.

To adapt this study change, one new analysis set is added for the efficacy analysis.

The populations for analysis are defined in Table 2 below.

Table 2: Description of analysis sets used to analyze the data in the study.

Analysis Sets	Description
Enrolled	All participants who sign the ICF
Randomized	The randomized analysis set includes all participants who were randomized in the study.
Full Analysis Set (FAS)	The FAS includes all randomized participants who received at least 1 dose of any study intervention.
Full Analyses Set for Week 52 (FASC52)	The FASC52 includes all randomized participants who received at least 1 dose of any study intervention and have the opportunity to complete the Week 52 visit prior to study termination
Safety	The safety analysis set includes all participants who received at least 1 dose of any study intervention.

Table 2: Description of analysis sets used to analyze the data in the study.

Analysis Sets	Description
Pharmacokinetics Analysis Set	The PK analysis set is defined as participants who received at least 1 dose of any active study intervention and have at least 1 valid post initial dose blood sample drawn for PK analysis.
Immunogenicity Analysis Set	The immunogenicity analysis set is defined as all participants who received at least 1 dose of active study intervention and have at least 1 post initial dose sample collection.
Biomarker Analysis Set	The biomarker analysis set is defined as participants who received at least 1 dose of any study intervention and have at least one sample for biomarker analysis

5. STATISTICAL ANALYSES

Early Termination Note: Due to the Sponsor's decision to stop screening of new participants as a result of enrollment challenges, fewer than 60 participants will be enrolled in the study. The end of study will occur after all enrolled participants have completed the Week 20 visit or discontinued study intervention prior to Week 24, and all participants have completed their final efficacy and safety visits per the SoA.

The statistical analyses section below is the originally planned analyses section. The analyses to be summarized in the study CSR will be noted at the beginning of each section below. For efficacy analyses, only the primary and secondary endpoints will be included in the CSR. Selected PK and biomarker analyses will be included in the CSR. All safety information collected will be summarized in the CSR. See below for details.

5.1. General Considerations

The statistical analyses will include all analyses from Week 0 through Week 60 (the final safety follow-up).

In general, baseline is defined as the last observation prior to or at the time of the first study agent administration, unless otherwise specified.

5.1.1. Visit Windows

Unless otherwise specified, nominal visits will be used for all by visit analyses. The study visits scheduled after randomization should occur at the time delineated in the SoA.

5.1.2. Pooling Algorithm for Analysis Centers

Unless otherwise specified, data from all investigational centers/sites will be pooled for analyses.

5.1.3. Reference Date, Study Day and Relative Day

The Reference Date is the date of the first study agent administration. If the date of the first study agent administration is missing or the first study agent administration is not done, then the Reference Date equals the corresponding visit date (eg, Week 0 visit date). If the corresponding visit date is also missing, then the Reference Date equals the randomization date.

Study Day 1 or Day 1 refers to the reference date (there is no Study Day 0). All efficacy and safety assessments at all visits will be assigned a day relative to this date.

5.2. Participant Dispositions

Screened participants and reason for screen failures will be summarized overall.

The number of participants in the following disposition categories will be summarized throughout the study by intervention group and overall:

- Participants randomized
- Participants who received study intervention
- Participants who completed the study
- Participants who discontinued study intervention
  - Reasons for discontinuation of study intervention (including discontinuation due to COVID-19 related reasons)
- Participants who terminated study prematurely
  - Reasons for termination of study (including termination due to COVID-19 related reasons)

The above categories will include summaries through the end of study.

A listing of participants will be provided for the following categories:

- Participants who discontinued study intervention
- Participants who terminated study participation prematurely
- Participants who were unblinded during the study period
- Participants who were randomized but did not receive study intervention.

5.3. Primary Endpoint Analysis

Early Termination Note: Due to the Sponsor's decision to stop screening of new participants as a result of enrollment challenges, fewer than 60 participants will be enrolled in the study. The end of study will occur after all enrolled participants have completed the Week 20 visit or discontinued study intervention prior to Week 24, and all participants have completed their final efficacy and safety visits per the SoA.

For the CSR, the analysis of the primary composite estimand (Section 5.3.2.1) will be performed using the analysis method specified in Section 5.3.3. All other analyses that are described in this section will not be performed for the CSR.

5.3.1. Definition of Endpoint(s)

The primary endpoint is the proportion of participants achieving at least 50% decrease in proteinuria from baseline at Week 24. Proteinuria is based on UPCR.

Variable specific data handling rules: Observed data will be used for the analysis.

5.3.2. Estimands

Primary Trial Objective: To evaluate the efficacy of guselkumab in participants with active LN on standard-of-care.

Estimand Scientific Question of Interest: What is the proportion of participants considered to have benefited from guselkumab versus placebo for the pre-specified duration (24 weeks), administered together with the protocol-allowed background standard-of-care medication?

5.3.2.1. Primary Estimand (Composite Estimand)

a. Study intervention:

- Guselkumab (experimental treatment/intervention) in addition to standard-of-care
- Placebo in addition to standard-of-care

b. **Population:** Participants between 18 and 75 with active LN (defined by meeting the classification criteria for SLE by the 2019 European League Against Rheumatism (EULAR)/ACR, having a Class III or IV predominant kidney biopsy documentation of ISN/RPS proliferative nephritis within the last 6 months prior to or during screening despite receiving one or more standard-of-care treatments.

c. **Variable**: Responder binary variable, defined as a participant achieving at least 50% decrease in proteinuria from baseline at Week 24 who does not:

- discontinue study intervention for any reason excluding COVID-19 related discontinuations or
- meet the Medication Intercurrent Event in Section (e) below

d. **Summary measure (Population-level summary)**: Difference in proportion between the study interventions

e. Intercurrent events and their corresponding strategies:

Intercurrent Events	**Strategy for Addressing Intercurrent Events and Its Description**
Discontinuation (DC) of study intervention for any reason excluding COVID-19 related discontinuations	**Composite Strategy:** A participant with this intercurrent event is considered to not have achieved at least 50% decrease in proteinuria after this event, the occurrence of this intercurrent event being captured in the variable definition.

Medication Intercurrent Event 1. Exceeding baseline glucocorticoid dose 2. Increase above 10 mg/d prednisone equivalent after Week 12, use of new or increased dose of concomitant medication related to LN or other immunosuppressive agents, within 8 weeks prior to the endpoint 3. Initiation of prohibited medications at any time prior to the endpoint Note: adjustments in glucocorticoids are permitted up to and including Week 12. Nonsystemic glucocorticoids, NSAIDs, antimalarials and topical agents will not be considered an intercurrent event.	**Composite Strategy:** Same as above

5.3.2.2. Supplementary Estimand 1 (Hypothetical)

a. Study intervention:

- Guselkumab (experimental treatment/intervention) in addition to standard-of-care
- Placebo in addition to standard-of-care

b. **Population:** Participants between 18 and 75 with active LN (defined by meeting the classification criteria for SLE by the 2019 European League Against Rheumatism (EULAR)/ACR, having a Class III-IV kidney biopsy documentation of ISN/RPS proliferative nephritis within the last 6 months prior to or during screening despite receiving one or more standard-of-care treatments.

c. **Variable**: Responder binary variable, defined as a participant achieving at least 50% decrease in proteinuria from baseline at Week 24

d. **Summary measure (Population-level summary)**: Difference in proportion between the study interventions

e. Intercurrent events and their corresponding strategies:

Intercurrent Events	**Strategy for Addressing Intercurrent Events and Its Description**
Discontinuation (DC) of study intervention for any reason excluding COVID-19 related discontinuations	**Hypothetical strategy:** The intercurrent event is addressed with a hypothetical strategy, as if these intercurrent events would not have occurred.
Medication Intercurrent Event	**Hypothetical Strategy:** Same as above

1. Exceeding baseline glucocorticoid dose 2. Increase above 10 mg/d prednisone equivalent after Week 12, use of new or increased dose of concomitant medication related to LN or other immunosuppressive agents, within 8 weeks prior to the endpoint 3. Initiation of prohibited medications at any time prior to the endpoint Note: adjustments in glucocorticoids are permitted up to and including Week 12. Nonsystemic glucocorticoids, NSAIDs, antimalarials and topical agents will not be considered an intercurrent event.	
	Note: Data after the intercurrent event will not be utilized in the analysis

Difference from Primary Estimand: The strategy to address the intercurrent events is to assume that participants with this intercurrent event is considered to have missing data at and after the event occurred instead of not having achieved at least 50% decrease in proteinuria after this event as in the primary estimand.

5.3.2.3. Supplementary Estimand 2 (Treatment Policy (de Facto))

a. Study intervention:

- Guselkumab (experimental treatment/intervention) in addition to standard-of-care
- Placebo in addition to standard-of-care

b. **Population:** Participants between 18 and 75 with active LN (defined by meeting the classification criteria for SLE by the 2019 European League Against Rheumatism (EULAR)/ACR, having a Class III-IV kidney biopsy documentation of ISN/RPS proliferative nephritis within the last 6 months prior to or during screening despite receiving one or more standard-of-care treatments.

c. **Variable**: Responder binary variable, defined as a participant achieving at least 50% decrease in proteinuria from baseline at Week 24

d. **Summary measure (Population-level summary)**: Difference in proportion between the study interventions

e. Intercurrent events and their corresponding strategies:

Intercurrent Events	Strategy for Addressing Intercurrent Events and Its Description

Discontinuation (DC) of study intervention for any reason excluding COVID-19 related discontinuations	**Treatment Policy Strategy:** The intercurrent event addressed with a treatment policy strategy, targeting the effect of the assignment to the treatment group, regardless of the occurrence of the intercurrent events.
Medication Intercurrent Event 1. Exceeding baseline glucocorticoid dose 2. Increase above 10 mg/d prednisone equivalent after Week 12, use of new or increased dose of concomitant medication related to LN or other immunosuppressive agents, within 8 weeks prior to the endpoint 3. Initiation of prohibited medications at any time prior to the endpoint Note: adjustments in glucocorticoids are permitted up to and including Week 12. Nonsystemic glucocorticoids, NSAIDs, antimalarials and topical agents will not be considered an intercurrent event.	**Treatment Policy Strategy:** Same as above
	Note: Under the Treatment Policy strategy, all data are utilized/used, regardless of the occurrence of an intercurrent event.

Difference from Primary Estimand: The strategy to address the intercurrent events is that the intercurrent events do not affect the outcome, and the data collected at and after the event will be used for analysis, instead of assuming participants have not achieved at least 50% decrease in proteinuria after the event as in the primary estimand.

5.3.2.4. Supplementary Estimand 3 (Composite)

a. Study intervention:

- Guselkumab (experimental treatment/intervention) in addition to standard-of-care
- Placebo in addition to standard-of-care

b. **Population:** Participants between 18 and 75 with active LN (defined by meeting the classification criteria for SLE by the 2019 European League Against Rheumatism (EULAR)/ACR, having a Class III or IV predominant kidney biopsy documentation of ISN/RPS proliferative nephritis within the last 6 months prior to or during screening despite receiving one or more standard-of-care treatments.

c. **Variable**: Responder binary variable, defined as a participant achieving at least 50% decrease in proteinuria from baseline at Week 24 who does not:

- discontinue study intervention for any reason excluding COVID-19 related discontinuations or
- meet the Medication Intercurrent Event in Section (e) below

d. **Summary measure (Population-level summary)**: Difference in proportion between the study interventions

e. Intercurrent events and their corresponding strategies:

Intercurrent Events	Strategy for Addressing Intercurrent Events and Its Description
Discontinuation (DC) of study intervention for worsening of LN	**Composite Strategy:** A participant with this intercurrent event is considered to not have achieved at least 50% decrease in proteinuria after this event, the occurrence of this intercurrent event being captured in the variable definition.
Medication Intercurrent Event 1. Exceeding baseline glucocorticoid dose 2. Increase above 10 mg/d prednisone equivalent after Week 12, use of new or increased dose of concomitant medication related to LN or other immunosuppressive agents, within 8 weeks prior to the endpoint 3. Initiation of prohibited medications at any time prior to the endpoint Note: adjustments in glucocorticoids are permitted up to and including Week 12. Nonsystemic glucocorticoids, NSAIDs, antimalarials and topical agents will not be considered an intercurrent event.	**Composite Strategy:** Same as above

Difference from Primary Estimand: The intercurrent event "discontinuation of study intervention for any reason" is changed to "discontinuation of study intervention for worsening of LN".

5.3.2.5. Supplementary Estimand 4 (Composite)

a. Study intervention:

- Guselkumab (experimental treatment/intervention) in addition to standard-of-care
- Placebo in addition to standard-of-care

b. **Population:** Participants between 18 and 75 with active LN (defined by meeting the classification criteria for SLE by the 2019 European League Against Rheumatism (EULAR)/ACR, having a Class III or IV predominant kidney biopsy documentation of ISN/RPS proliferative nephritis within the last 6 months prior to or during screening despite receiving one or more standard-of-care treatments.

c. **Variable**: Responder binary variable, defined as a participant achieving at least 50% decrease in proteinuria from baseline at Week 24 who does not:

- discontinue study intervention for any reason or
- meet the Medication Intercurrent Event in Section (e) below

d. **Summary measure (Population-level summary)**: Difference in proportion between the study interventions

e. Intercurrent events and their corresponding strategies:

Intercurrent Events	**Strategy for Addressing Intercurrent Events and Its Description**
Discontinuation (DC) of study intervention for any reason excluding COVID-19 related discontinuations	**Composite Strategy:** A participant with this intercurrent event is considered to not have achieved at least 50% decrease in proteinuria after this event, the occurrence of this intercurrent event being captured in the variable definition.
Medication Intercurrent Event 1. Exceeding baseline glucocorticoid dose 2. Increase above 10 mg/d prednisone equivalent after Week 12, use of new or increased dose of concomitant medication related to LN or other immunosuppressive agents, within 8 weeks prior to the endpoint 3. Initiation of prohibited medications at any time prior to the endpoint Note: adjustments in glucocorticoids are permitted up to and including Week 12. Nonsystemic glucocorticoids, NSAIDs, antimalarials and topical agents will not be considered an intercurrent event.	**Composite Strategy:** Same as above
Discontinued study intervention due to COVID-19 related reasons	**Hypothetical strategy:** The intercurrent event is addressed with a hypothetical strategy, as if these intercurrent events would not have occurred. Note: Data after the intercurrent event will not be utilized in the analysis

Difference from Primary Estimand: For discontinuations due to COVID-19 related event or situations, the participant's data after the event will not be used after the intercurrent event.

5.3.2.6. Supplementary Estimand 5 (Composite)

a. Study intervention:

- Guselkumab (experimental treatment/intervention) in addition to standard-of-care
- Placebo in addition to standard-of-care

b. **Population:** Participants between 18 and 75 with active LN (defined by meeting the classification criteria for SLE by the 2019 European League Against Rheumatism (EULAR)/ACR, having a Class III or IV predominant kidney biopsy documentation of

ISN/RPS proliferative nephritis within the last 6 months prior to or during screening despite receiving one or more standard-of-care treatments.

c. **Variable**: Responder binary variable, defined as a participant achieving at least 50% decrease in proteinuria from baseline at Week 24 who does not:
   - discontinue study intervention for any reason excluding COVID-19 related discontinuations or
   - meet the Medication Intercurrent Event in Section (e) below

d. **Summary measure (Population-level summary)**: Difference in proportion between the study interventions

e. **Intercurrent events and their corresponding strategies:**

Intercurrent Events	**Strategy for Addressing Intercurrent Events and Its Description**
Discontinuation (DC) of study intervention for any reason excluding COVID-19 related discontinuations	**Composite Strategy:** A participant with this intercurrent event is considered to not have achieved at least 50% decrease in proteinuria after this event, the occurrence of this intercurrent event being captured in the variable definition.
Medication Intercurrent Event 1. Exceeding baseline glucocorticoid dose 2. Increase above 10 mg/d prednisone equivalent after Week 12, use of new or increased dose of concomitant medication related to LN or other immunosuppressive agents 3. Initiation of prohibited medications at any time prior to the endpoint Note: adjustments in glucocorticoids are permitted up to and including Week 12. Nonsystemic glucocorticoids, NSAIDs, antimalarials and topical agents will not be considered an intercurrent event.	**Composite Strategy:** Same as above

4. **Difference from Primary Estimand:** The first Medication Intercurrent Event, "Increase above 10 mg/d prednisone equivalent, use of new or increased dose of concomitant medication related to LN or other immunosuppressive agents" can occur at any time after Week 12, not just within 8 weeks prior to the endpoint.

5.3.3. Analysis Methods

Unless otherwise specified, the population for analysis will be the FAS defined in Section 4 for the primary and its respective sensitivity analyses.

Simple descriptive statistics, such as n, mean, standard deviation (SD), median, interquartile (IQ) range, minimum and maximum for continuous variables and counts and percentages for discrete variables will be used to summarize most data.

For the primary analysis, the primary composite estimand will be targeted.

Generalized linear model with logit link for a binary mixed effects repeated measures model (MMRM) will be used to analyze the data. The model will include all available observed data after applying intercurrent events with treatment, visit, region, baseline UPCR level (<3 mg/mg and ≥3 mg/mg), and treatment and visit interaction in the model will be used to analyze the data. The 1-sided p-value from the difference in proportion of participants with ≥50% decrease in proteinuria from baseline at Week 24 between the intervention groups will be provided. In addition, the estimate and its 80% confidence interval (CI) estimated from the model will also be provided.

5.3.4. Supplementary Analyses

5.3.4.1. Supplementary Analysis 1 (Supplementary Estimand 1 (Hypothetical))

The primary endpoint will be analyzed using the Supplementary Estimand 1 (Hypothetical). A Cochran-Mantel-Haenszel (CMH) test stratified by region, baseline UPCR level (<3 mg/mg, ≥3 mg/mg) will be used to analyze the data. An 80% CI for the difference in study intervention will be provided based on the Wald statistic.

5.3.4.2. Supplementary Analysis 2 (Supplementary Estimand 1 (Hypothetical))

The primary endpoint will be analyzed using the Supplementary Estimand 1 (Hypothetical). Missing data will be imputed using multiple imputation methods. The imputation model will include study intervention, region, baseline UPCR level (<3 mg/mg and ≥3 mg/mg), race (African vs non-African) as covariates. 300 imputed datasets will be created. A CMH test stratified by region, baseline UPCR level (< 3 mg/mg, ≥3 mg/mg) will be used to obtain the CMH test statistic for each imputed dataset. A Wilson Hilferty transformation was used to aggregate estimates and obtain overall p-value for the CMH test.

5.3.4.3. Supplementary Analysis 3 (Supplementary Estimand 2 (Treatment Policy))

The primary endpoint will be analyzed utilizing the Supplementary Estimand 2 (Treatment Policy). The analysis method for the primary analysis in Section 5.3.3 will be used.

5.3.4.4. Supplementary Analysis 4 (Supplementary Estimand 3 (Composite))

The primary endpoint will be analyzed utilizing the Supplementary Estimand 3 (Composite). The analysis method for the primary analysis in Section 5.3.3 will be used.

5.3.4.5. Supplementary Analysis 5 (Supplementary Estimand 4 (Composite))

The primary endpoint will be analyzed utilizing the Supplementary Estimand 4 (Composite). The analysis method for the Supplementary Analysis 1 (Section 5.3.4.1) will be used.

5.3.4.6. Supplementary Analysis 6 (Supplementary Estimand 5 (Composite))

The primary endpoint will be analyzed utilizing the Supplementary Estimand 5 (Composite). The analysis method for the primary analysis in Section 5.3.3 will be used.

5.3.5. Sensitivity Analyses

5.3.5.1. Sensitivity Analysis 1 (Primary Composite Estimand)

"Tipping Point" via exhaustive scenarios will be used. A two-dimensional tipping point analysis of exhaustive scenarios for all missing data at Week 24 will be performed on the primary endpoint to evaluate the missing at random assumption for the Composite Estimand. For participants with missing proteinuria data at Week 24, the data will be imputed in an increasing manner by participant for each treatment intervention. Specifically, imputation starts where all participants do not achieve 50% decrease in proteinuria up to the scenario where all participants achieved 50% decrease in proteinuria. This would include all possible scenarios including scenarios where participants on guselkumab have worse outcomes than participants on placebo. The analysis method for the primary analysis in Section 5.3.3 will be used.

5.3.5.2. Sensitivity Analysis 2 (Supplementary Estimand 2 (Treatment Policy))

"Tipping Point" via exhaustive scenarios as in Sensitivity Analysis 1 will be performed on the Supplementary Estimand 2 (Treatment Policy). The analysis method for the primary analysis in Section 5.3.3 will be used.

5.4. Secondary Endpoint(s) Analysis

Early Termination Note: Due to the Sponsor's decision to stop screening of new participants as a result of enrollment challenges, fewer than 60 participants will be enrolled in the study. The end of study will occur after all enrolled participants have completed the Week 20 visit or discontinued study intervention prior to Week 24, and all participants have completed their final efficacy and safety visits per the SoA.

For secondary endpoints in the CSR, only analysis of the main estimand for each secondary endpoint that is listed below will be performed using the analysis methods specified in Sections 5.4.2.3.1 and 5.4.2.3.2:

- Proportion of participants achieving complete renal response (CRR) at Week 24 (Section 5.4.2.2.1)
- Proportion of participants achieving a sustained reduction in steroid dose ≤10 mg/day of prednisone or equivalent from Week 16 to Week 24 (Section 5.4.2.2.2.1)
- Proportion of participants achieving at least 50% decrease in proteinuria from baseline at Week 52 (Section 5.4.2.2.3.1)
- Proportion of participants achieving CRR at Week 52 (Section 5.4.2.2.4.1)
- Proportion of participants with UPCR <0.5 mg/mg at Week 24 (Section 5.4.2.2.5)
- Proportion of participants with UPCR <0.75 mg/mg at Week 24 (Section 5.4.2.2.6)
- Time to achievement of CRR (Section 5.4.2.2.7.1)
- Time to treatment failure (TF) (Section 5.4.2.2.8)

The analysis population will be the FAS except for the endpoints at Week 52, for which the FASC52 analysis set will be used.

All other analyses that are described in this section will not be performed for the CSR.

5.4.1. Multiplicity Adjustment for Testing Procedures

No multiplicity adjustments will be made for any testing procedures.

5.4.2. Key Confirmatory Secondary Endpoint(s)

Objective: To evaluate the efficacy of guselkumab in participants with active LN

The secondary endpoints are the following:

1. Proportion of participants achieving complete renal response (CRR) at Week 24
2. Proportion of participants achieving a sustained reduction in steroid dose ≤10 mg/day of prednisone or equivalent from Week 16 to Week 24
3. Proportion of participants achieving at least 50% decrease in proteinuria from baseline at Week 52
4. Proportion of participants achieving CRR at Week 52
5. Proportion of participants with UPCR <0.5 mg/mg at Week 24
6. Proportion of participants with UPCR <0.75 mg/mg at Week 24
7. Time to achievement of CRR
8. Time to treatment failure (TF)

5.4.2.1. Definition of Endpoint(s)

5.4.2.1.1. Complete Renal Response (CRR)

Complete renal response (CRR) is defined as :

-Urine Protein to Creatinine Ratio (UPCR) <0.5 mg/mg (alternative thresholds of 0.75, and possibly others will be examined, separately).

AND

– Estimated Glomerular Filtration Rate (eGFR) ≥60 mL/min/m^2 or no confirmed decrease ≥20% from baseline.

AND

– Prednisone dose ≤10 mg/d.

5.4.2.1.2. Complete Renal Response 50% Pred (CRR – 50% Pred)

Complete Renal Response 50% Pred is defined as CRR above (Section 5.4.2.1.1 except for prednisone dose, whereby if a participant enters the study with baseline prednisone of 10 mg/d, then the prednisone dose must be <10 mg/d with at least a 50% reduction in dose.

5.4.2.1.3. Glucocorticoid (Prednisone or Prednisone Equivalent) Reduction

1. Participants with a sustained reduction in steroid dose ≤10 mg/day of prednisone or equivalent are participants who sustained a continuous reduction in steroid to ≤10 mg/day of prednisone or equivalent for the time duration measured.

   The average daily dose for any given day is the average of the last available (non-missing) values within 7 days, including the day of interest.

2. Reduction of glucocorticoid dose is defined as:

   - A reduction in average daily oral glucocorticoid dose down to ≤10 mg/day by Week 12

     and

   - at least a 50% decrease from baseline dose.

3. Other considerations to meet sustained reduction of glucocorticoid dose include

   Dose adjustments after starting reduction of glucocorticoid dose are permitted and participants will still be considered to have sustained reduction unless they return to or exceed their baseline (Week 0) dose. These dose adjustments are permitted up to the Week 12 visit only.

   Note: 10 mg of prednisone equivalent is used here although the tapering target is 5 mg. Dose increases above 10 mg of prednisone equivalent or above 50% of baseline dose after Week 12 will not be considered as sustained reduction in glucocorticoids.

5.4.2.1.4. Time to Achievement of Complete Renal Response (CRR)

Time to achievement of CRR is defined as the time to the first observation of CRR from baseline.

5.4.2.1.5. Time to Treatment Failure (TF)

Time to TF is defined as time to the first occurrence of TF from baseline. TF is defined as the intercurrent events for the Supplementary Composite Estimand 5 of the primary endpoint in Section 5.3.2.6.

5.4.2.2. Estimand(s)

5.4.2.2.1. Proportion of Participants Achieving Complete Renal Response (CRR) at Week 24

Composite Estimand
1. Study intervention:

- Guselkumab (experimental treatment/intervention) in addition to standard-of-care
- Placebo in addition to standard-of-care

2. Population: Participants between 18 and 75 with active LN (defined by meeting the classification criteria for SLE by the 2019 European League Against Rheumatism (EULAR)/ACR, having a Class III-IV kidney biopsy documentation of ISN/RPS proliferative nephritis within the last 6 months prior to or during screening despite receiving one or more standard-of-care treatments.

3. Variable: Responder binary variable, defined as a participant achieving Complete Renal Response (CRR) at Week 24 who does not:

- discontinue study intervention for any reason excluding COVID-19 related discontinuations or
- meet the Medication Intercurrent Event in Section (5) below

4. Summary measure (Population-level summary): Difference in proportion between the study interventions

5. Intercurrent events and their corresponding strategies:

Intercurrent Events	**Strategy for Addressing Intercurrent Events and Its Description**
Discontinuation (DC) of study intervention for any reason excluding COVID-19 related discontinuations	**Composite Strategy:** A participant with this intercurrent event is considered to not have achieved CRR after this event, the occurrence of this intercurrent event being captured in the variable definition.
<u>Medication Intercurrent Event</u> 1. Exceeding baseline glucocorticoid dose 2. Increase above 10 mg/d prednisone equivalent after Week 12, use of new or increased dose of concomitant medication related to LN or other immunosuppressive agents, within 8 weeks prior to the endpoint 3. Initiation of prohibited medications at any time prior to the endpoint Note: adjustments in glucocorticoids are permitted up to and including Week 12. Nonsystemic glucocorticoids, NSAIDs, antimalarials and topical agents will not be considered an intercurrent event.	**Composite Strategy:** Same as above

5.4.2.2.2. Proportion of Participants Achieving a Sustained Reduction in Steroid Dose ≤10 mg/day of Prednisone or Equivalent from Week 16 to Week 24

5.4.2.2.2.1. Main Estimand (Composite)

1. Study intervention:

- Guselkumab (experimental treatment/intervention) in addition to standard-of-care
- Placebo in addition to standard-of-care

2. Population: Participants between 18 and 75 with active LN (defined by meeting the classification criteria for SLE by the 2019 European League Against Rheumatism (EULAR)/ACR, having a Class III-IV kidney biopsy documentation of ISN/RPS proliferative nephritis within the last 6 months prior to or during screening despite receiving one or more standard-of-care treatments.

3. Variable: Responder binary variable, defined as a participant achieving a sustained reduction in steroid dose ≤10 mg/day of prednisone or equivalent from Week 16 to Week 24

4. Summary measure (Population-level summary): Difference in proportion between the study interventions

5. Intercurrent events and their corresponding strategies:

Intercurrent Events	**Strategy for Addressing Intercurrent Events and Its Description**
Discontinuation (DC) of study intervention for any reason excluding COVID-19 related discontinuations	**Composite Strategy:** A participant with this intercurrent event is considered to not have achieved Sustained Reduction in Steroid Dose after this event, the occurrence of this intercurrent event being captured in the variable definition.
Medication Intercurrent Event 1. Initiation of prohibited medications at any time prior to the endpoint Note: Nonsystemic glucocorticoids, NSAIDs, antimalarials and topical agents will not be considered an intercurrent event.	**Composite Strategy:** Same as above

5.4.2.2.2.2. Supplementary Estimand (Treatment Policy (de Facto))

All attributes (1-4) of the supplementary estimand are the same as above main estimand (Section 5.4.2.2.2.1) except for the intercurrent events, where a treatment policy strategy is used instead.

5. Intercurrent events and their corresponding strategies:

Intercurrent Events	Strategy for Addressing Intercurrent Events and Its Description
Discontinuation (DC) of study intervention for any reason excluding COVID-19 related discontinuations	**Treatment Policy Strategy:** The intercurrent event addressed with a treatment policy strategy, targeting the effect of the assignment to the treatment group, regardless of the occurrence of the intercurrent events.
Medication Intercurrent Event 1. Initiation of prohibited medications at any time prior to the endpoint Note: Nonsystemic glucocorticoids, NSAIDs, antimalarials and topical agents will not be considered an intercurrent event.	**Treatment Policy Strategy:** Same as above
	Note: Under the Treatment Policy strategy, all data are utilized/used, regardless of the occurrence of an intercurrent event.

Difference from Main Estimand: The treatment policy strategy is used instead of the composite strategy.

5.4.2.2.3. Proportion of Participants Achieving at Least 50% Decrease in Proteinuria from Baseline at Week 52

5.4.2.2.3.1. Main Estimand

1. Study intervention:

- Guselkumab (experimental treatment/intervention) in addition to standard-of-care
- Placebo in addition to standard-of-care

2. Population: Participants between 18 and 75 with active LN (defined by meeting the classification criteria for SLE by the 2019 European League Against Rheumatism (EULAR)/ACR, having a Class III-IV kidney biopsy documentation of ISN/RPS proliferative nephritis within the last 6 months prior to or during screening despite receiving one or more standard-of-care treatments.

3. Variable: Responder binary variable, defined as a participant achieving at least 50% decrease in proteinuria from baseline at Week 52 who does not:

- discontinue study intervention for any reason excluding COVID-19 related discontinuations or
- meet the Medication Intercurrent Event in Section (5) below

4. Summary measure (Population-level summary): Difference in proportion between the study interventions

5. Intercurrent events and their corresponding strategies:

Intercurrent Events	**Strategy for Addressing Intercurrent Events and Its Description**
Discontinuation (DC) of study intervention for any reason excluding COVID-19 related discontinuations	**Composite Strategy:** A participant with this intercurrent event is considered to not have achieved 50% decrease in proteinuria after this event, the occurrence of this intercurrent event being captured in the variable definition.
Medication Intercurrent Event 1. Exceeding baseline glucocorticoid dose 2. Increase above 10 mg/d prednisone equivalent after Week 12, use of new or increased dose of concomitant medication related to LN or other immunosuppressive agents, within 8 weeks prior to the endpoint 3. Initiation of prohibited medications at any time prior to the endpoint Note: adjustments in glucocorticoids are permitted up to and including Week 12. Nonsystemic glucocorticoids, NSAIDs, antimalarials and topical agents will not be considered an intercurrent event.	**Composite Strategy:** Same as above
Sustained increase of prednisone equivalent between Week 24 and Week 44 is allowed up to 40 mg/d for ≤10 days once for non-SLE/LN treatment (eg, COPD, asthma, contact dermatitis).	**Treatment Policy Strategy:** The intercurrent event addressed with a treatment policy strategy, targeting the effect of the assignment to the treatment group, regardless of the occurrence of the intercurrent events.
	Note: Under the Treatment Policy strategy, all data are utilized/used, regardless of the occurrence of an intercurrent event.

5.4.2.2.3.2. Supplementary Estimand

All attributes (1-4) of the supplementary estimand are the same as above main estimand (Section 5.4.2.2.3.1) except for the intercurrent events, where the treatment policy strategy is omitted.

5. Intercurrent events and their corresponding strategies:

Intercurrent Events	Strategy for Addressing Intercurrent Events and Its Description
Discontinuation (DC) of study intervention for any reason excluding COVID-19 related discontinuations	**Composite Strategy:** A participant with this intercurrent event is considered to not have achieved 50% decrease in proteinuria after this event, the occurrence of this intercurrent event being captured in the variable definition.
Medication Intercurrent Event 1. Exceeding baseline glucocorticoid dose 2. Increase above 10 mg/d prednisone equivalent after Week 12, use of new or increased dose of concomitant medication related to LN or other immunosuppressive agents within 8 weeks prior to the endpoint 3. Initiation of prohibited medications at any time prior to the endpoint Note: adjustments in glucocorticoids are permitted up to and including Week 12. Nonsystemic glucocorticoids, NSAIDs, antimalarials and topical agents will not be considered an intercurrent event.	**Composite Strategy:** Same as above

Difference from Main Estimand: Participants with sustained increase of prednisone equivalent between Week 24 and Week 44 will not be allowed up to 40 mg/d for ≤10 days once for non-SLE/LN treatment (eg, COPD, asthma, contact dermatitis), and will not achieve CRR after the event.

5.4.2.2.4. Proportion of Participants Achieving CRR at Week 52

5.4.2.2.4.1. Main estimand

1. Study intervention:

- Guselkumab (experimental treatment/intervention) in addition to standard-of-care
- Placebo in addition to standard-of-care

2. Population: Participants between 18 and 75 with active LN (defined by meeting the classification criteria for SLE by the 2019 European League Against Rheumatism (EULAR)/ACR, having a Class III-IV kidney biopsy documentation of ISN/RPS proliferative nephritis within the last 6 months prior to or during screening despite receiving one or more standard-of-care treatments.

3. Variable: Responder binary variable, defined as a participant achieving CRR at Week 52 who does not:

- discontinue study intervention for any reason excluding COVID-19 related discontinuations or
- meet the Medication Intercurrent Event in Section (5) below

4. Summary measure (Population-level summary): Difference in proportion between the study interventions

5. Intercurrent events and their corresponding strategies:

Intercurrent Events	**Strategy for Addressing Intercurrent Events and Its Description**
Discontinuation (DC) of study intervention for any reason excluding COVID-19 related discontinuations	**Composite Strategy:** A participant with this intercurrent event is considered to not have achieved CRR after this event, the occurrence of this intercurrent event being captured in the variable definition.
Medication Intercurrent Event 1. Exceeding baseline glucocorticoid dose 2. Increase above 10 mg/d prednisone equivalent after Week 12, use of new or increased dose of concomitant medication related to LN or other immunosuppressive agents, within 8 weeks prior to the endpoint 3. Initiation of prohibited medications at any time prior to the endpoint Note: adjustments in glucocorticoids are permitted up to and including Week 12. Nonsystemic glucocorticoids, NSAIDs, antimalarials and topical agents will not be considered an intercurrent event.	**Composite Strategy:** Same as above
Sustained increase of prednisone equivalent between Week 24 and Week 44 is allowed up to 40 mg/d for ≤10 days once for non-SLE/LN treatment (eg, COPD, asthma, contact dermatitis).	**Treatment Policy Strategy:** The intercurrent event addressed with a treatment policy strategy, targeting the effect of the assignment to the treatment group, regardless of the occurrence of the intercurrent events.
	Note: Under the Treatment Policy strategy, all data are utilized/used, regardless of the occurrence of an intercurrent event.

5.4.2.2.4.2. Supplementary Estimand 1

All attributes (1-4) of the supplementary estimand are the same as above main estimand (Section 5.4.2.2.4.1) except for the intercurrent events, where the treatment policy strategy is omitted.

5. Intercurrent events and their corresponding strategies:

Intercurrent Events	Strategy for Addressing Intercurrent Events and Its Description
Discontinuation (DC) of study intervention for any reason excluding COVID-19 related discontinuations	**Composite Strategy:** A participant with this intercurrent event is considered to not have achieved CRR after this event, the occurrence of this intercurrent event being captured in the variable definition.
Medication Intercurrent Event 1. Exceeding baseline glucocorticoid dose 2. Increase above 10 mg/d prednisone equivalent after Week 12, use of new or increased dose of concomitant medication related to LN or other immunosuppressive agents within 8 weeks prior to the endpoint 3. Initiation of prohibited medications at any time prior to the endpoint Note: adjustments in glucocorticoids are permitted up to and including Week 12. Nonsystemic glucocorticoids, NSAIDs, antimalarials and topical agents will not be considered an intercurrent event.	**Composite Strategy:** Same as above

Difference from Main Estimand: Participants with sustained increase of prednisone equivalent between Week 24 and Week 44 will not be allowed up to 40 mg/d for ≤10 days once for non-SLE/LN treatment (eg, COPD, asthma, contact dermatitis), and will not achieve CRR after the event.

5.4.2.2.4.3. Supplementary Estimand 2

All attributes (1-4) of the supplementary estimand are the same as above main estimand (Section 5.4.2.2.4.1) except for the intercurrent events, where a composite strategy is added for participants not achieving CRR due to intercurrent events at Week 24 will also be non-achievers through Week 52.

Intercurrent Events	Strategy for Addressing Intercurrent Events and Its Description
Participants who do not achieve CRR due to intercurrent events at Week 24 will also be non-achievers through Week 52	**Composite Strategy:** A participant with this intercurrent event is considered to not have achieved CRR after this event, the occurrence of this intercurrent event being captured in the variable definition.
Discontinuation (DC) of study intervention for any reason excluding COVID-19 related discontinuations	**Composite Strategy:** Same as above

Medication Intercurrent Event 1. Exceeding baseline glucocorticoid dose 2. Increase above 10 mg/d prednisone equivalent after Week 12, use of new or increased dose of concomitant medication related to LN or other immunosuppressive agents, within 8 weeks prior to the endpoint 3. Initiation of prohibited medications at any time prior to the endpoint Note: adjustments in glucocorticoids are permitted up to and including Week 12. Nonsystemic glucocorticoids, NSAIDs, antimalarials and topical agents will not be considered an intercurrent event.	**Composite Strategy:** Same as above
Sustained increase of prednisone equivalent between Week 24 and Week 44 is allowed up to 40 mg/d for ≤10 days once for non-SLE/LN treatment (eg, COPD, asthma, contact dermatitis).	**Treatment Policy Strategy:** The intercurrent event addressed with a treatment policy strategy, targeting the effect of the assignment to the treatment group, regardless of the occurrence of the intercurrent events.
	Note: Under the Treatment Policy strategy, all data are utilized/used, regardless of the occurrence of an intercurrent event.

Difference from Main Estimand: Participants who do not achieve CRR due to intercurrent events at Week 24 will also be non-achievers through Week 52.

5.4.2.2.4.4. Supplementary Estimand 3

All attributes (1-4) of the supplementary estimand are the same as above Main Estimand (Section 5.4.2.2.4.1) except for the intercurrent events, where the treatment policy strategy is omitted, and a composite strategy is added for participants not achieving CRR due to intercurrent events at Week 24 will also be non-achievers through Week 52.

5. Intercurrent events and their corresponding strategies:

Intercurrent Events	Strategy for Addressing Intercurrent Events and Its Description
Participants who do not achieve CRR due to intercurrent events at Week 24 will also be non-achievers through Week 52	**Composite Strategy:** A participant with this intercurrent event is considered to not have achieved CRR after this event, the occurrence of this intercurrent event being captured in the variable definition.
Discontinuation (DC) of study intervention for any reason excluding COVID-19 related discontinuations	**Composite Strategy:** Same as above
Medication Intercurrent Event 1. Exceeding baseline glucocorticoid dose 2. Increase above 10 mg/d prednisone equivalent after Week 12, use of new or increased dose of concomitant medication related to LN or other immunosuppressive agents within 8 weeks prior to the endpoint 3. Initiation of prohibited medications at any time prior to the endpoint Note: adjustments in glucocorticoids are permitted up to and including Week 12. Nonsystemic glucocorticoids, NSAIDs, antimalarials and topical agents will not be considered an intercurrent event.	**Composite Strategy:** Same as above

Difference from main estimand: Participants who do not achieve CRR due to intercurrent events at Week 24 will also be non-achievers through Week 52. In addition, participants with sustained increase of prednisone equivalent between Week 24 and Week 44 will not be allowed up to 40 mg/d for ≤10 days once for non-SLE/LN treatment (eg, COPD, asthma, contact dermatitis), and will not achieve CRR after the event.

5.4.2.2.5. Proportion of Participants with Urine Protein to Creatinine Ratio (UPCR) <0.5 mg/mg at Week 24

Composite Estimand

1. Study intervention:

- Guselkumab (experimental treatment/intervention) in addition to standard-of-care
- Placebo in addition to standard-of-care

2. Population: Participants between 18 and 75 with active LN (defined by meeting the classification criteria for SLE by the 2019 European League Against Rheumatism (EULAR)/ACR, having a Class III-IV kidney biopsy documentation of ISN/RPS proliferative nephritis within the last 6 months prior to or during screening despite receiving one or more standard-of-care treatments.

3. Variable: Responder binary variable, defined as a participant with UPCR <0.5 mg/mg at Week 24 who does not:

- discontinue study intervention for any reason excluding COVID-19 related discontinuations or
- meet the Medication Intercurrent Event in Section (5) below

4. Summary measure (Population-level summary): Difference in proportion between the study interventions

5. Intercurrent events and their corresponding strategies:

Intercurrent Events	**Strategy for Addressing Intercurrent Events and Its Description**
Discontinuation (DC) of study intervention for any reason excluding COVID-19 related discontinuations	**Composite Strategy:** A participant with this intercurrent event is considered to not have achieved UPCR <0.5 mg/mg after this event, the occurrence of this intercurrent event being captured in the variable definition.
Medication Intercurrent Event 1. Exceeding baseline glucocorticoid dose 2. Increase above 10 mg/d prednisone equivalent after Week 12, use of new or increased dose of concomitant medication related to LN or other immunosuppressive agents, within 8 weeks prior to the endpoint 3. Initiation of prohibited medications at any time prior to the endpoint Note: adjustments in glucocorticoids are permitted up to and including Week 12. Nonsystemic glucocorticoids, NSAIDs, antimalarials and topical agents will not be considered an intercurrent event.	**Composite Strategy:** Same as above

5.4.2.2.6. Proportion of Participants with UPCR <0.75 mg/mg at Week 24

Composite Estimand

1. Study intervention:

- Guselkumab (experimental treatment/intervention) in addition to standard-of-care
- Placebo in addition to standard-of-care

2. Population: Participants between 18 and 75 with active LN (defined by meeting the classification criteria for SLE by the 2019 European League Against Rheumatism (EULAR)/ACR, having a Class III-IV kidney biopsy documentation of ISN/RPS proliferative nephritis within the last 6 months prior to or during screening despite receiving one or more standard-of-care treatments.

3. Variable: Responder binary variable, defined as a participant with UPCR <0.75 mg/mg at Week 24 who does not:

- discontinue study intervention for any reason excluding COVID-19 related discontinuations or
- meet the Medication Intercurrent Event in Section (5) below

4. Summary measure (Population-level summary): Difference in proportion between the study interventions

5. Intercurrent events and their corresponding strategies:

Intercurrent Events	**Strategy for Addressing Intercurrent Events and Its Description**
Discontinuation (DC) of study intervention for any reason excluding COVID-19 related discontinuations	**Composite Strategy:** A participant with this intercurrent event is considered to not have achieved UPCR <0.75 mg/mg after this event, the occurrence of this intercurrent event being captured in the variable definition.
Medication Intercurrent Event	**Composite Strategy:** Same as above

1. Exceeding baseline glucocorticoid dose 2. Increase above 10 mg/d prednisone equivalent after Week 12, use of new or increased dose of concomitant medication related to LN or other immunosuppressive agents, within 8 weeks prior to the endpoint 3. Initiation of prohibited medications at any time prior to the endpoint Note: adjustments in glucocorticoids are permitted up to and including Week 12. Nonsystemic glucocorticoids, NSAIDs, antimalarials and topical agents will not be considered an intercurrent event.	

5.4.2.2.7. Time to Achievement of CRR through Week 24 and 52

5.4.2.2.7.1. Main Estimand

1. Study intervention:

- Guselkumab (experimental treatment/intervention) in addition to standard-of-care
- Placebo in addition to standard-of-care

2. Population: Participants between 18 and 75 with active LN (defined by meeting the classification criteria for SLE by the 2019 European League Against Rheumatism (EULAR)/ACR, having a Class III-IV kidney biopsy documentation of ISN/RPS proliferative nephritis within the last 6 months prior to or during screening despite receiving one or more standard-of-care treatments.

3. Variable: Time to CRR

4. Summary measure (Population-level summary): Hazard ratio of the guselkumab intervention group vs. the placebo intervention group

5. Intercurrent events and their corresponding strategies:

Intercurrent Events	**Strategy for Addressing Intercurrent Events and Its Description**
Discontinuation (DC) of study intervention for any reason excluding COVID-19 related discontinuations	**Composite Strategy:** A participant with this intercurrent event is considered to not have achieved CRR after this event, the occurrence of this intercurrent event being captured in the variable definition.
Medication Intercurrent Event	**Composite Strategy:** Same as above

1. Exceeding baseline glucocorticoid dose 2. Increase above 10 mg/d prednisone equivalent after Week 12, use of new or increased dose of concomitant medication related to LN or other immunosuppressive agents within 8 weeks prior to the endpoint 3. Initiation of prohibited medications at any time prior to the endpoint Note: adjustments in glucocorticoids are permitted up to and including Week 12. Nonsystemic glucocorticoids, NSAIDs, antimalarials and topical agents will not be considered an intercurrent event.	
Sustained increase of prednisone equivalent between Week 24 and Week 44 is allowed up to 40 mg/d for ≤10 days once for non-SLE/LN treatment (eg, COPD, asthma, contact dermatitis).	**Treatment Policy Strategy:** The intercurrent event addressed with a treatment policy strategy, targeting the effect of the assignment to the treatment group, regardless of the occurrence of the intercurrent events.
	Note: Under the Treatment Policy strategy, all data are utilized/used, regardless of the occurrence of an intercurrent event.

5.4.2.2.7.2. Supplementary Estimand 1 for Time to Achievement of CRR through Week 52

All attributes (1-4) of the supplementary estimand are the same as above (Section 5.4.2.2.7.1) except for the intercurrent events, where a composite strategy is added for participants not achieving CRR due to intercurrent events at Week 24 will also be non-achievers through Week 52.

5. Intercurrent events and their corresponding strategies:

Intercurrent Events	**Strategy for Addressing Intercurrent Events and Its Description**
Participants who do not achieve CRR due to intercurrent events at Week 24 will also be non-achievers through Week 52	**Composite Strategy:** A participant with this intercurrent event is considered to not have achieved CRR after this event, the occurrence of this intercurrent event being captured in the variable definition.
Discontinuation (DC) of study intervention for any reason excluding COVID-19 related discontinuations	**Composite Strategy:** Same as above
Medication Intercurrent Event	**Composite Strategy:** Same as above

4. Exceeding baseline glucocorticoid dose 5. Increase above 10 mg/d prednisone equivalent after Week 12, use of new or increased dose of concomitant medication related to LN or other immunosuppressive agents, within 8 weeks prior to the endpoint 6. Initiation of prohibited medications at any time prior to the endpoint Note: adjustments in glucocorticoids are permitted up to and including Week 12. Nonsystemic glucocorticoids, NSAIDs, antimalarials and topical agents will not be considered an intercurrent event.	
Sustained increase of prednisone equivalent between Week 24 and Week 44 is allowed up to 40 mg/d for ≤10 days once for non-SLE/LN treatment (eg, COPD, asthma, contact dermatitis).	**Treatment Policy Strategy:** The intercurrent event addressed with a treatment policy strategy, targeting the effect of the assignment to the treatment group, regardless of the occurrence of the intercurrent events.
	Note: Under the Treatment Policy strategy, all data are utilized/used, regardless of the occurrence of an intercurrent event.

Difference from Main Estimand: Participants who do not achieve CRR due to intercurrent events at Week 24 will also be non-achievers through Week 52.

5.4.2.2.7.3. Supplementary Estimand 2 for Time to Achievement of CRR through Week 52

All attributes (1-4) of the supplementary estimand are the same as above main estimand (Section 5.4.2.2.7.1) except for the intercurrent events, where only a composite strategy is used instead.

5. Intercurrent events and their corresponding strategies:

Intercurrent Events	**Strategy for Addressing Intercurrent Events and Its Description**
Discontinuation (DC) of study intervention for any reason excluding COVID-19 related discontinuations	**Composite Strategy:** A participant with this intercurrent event is considered to not have achieved CRR after this event, the occurrence of this intercurrent event being captured in the variable definition.
Medication Intercurrent Event	**Composite Strategy:** Same as above

1. Exceeding baseline glucocorticoid dose 2. Increase above 10 mg/d prednisone equivalent after Week 12, use of new or increased dose of concomitant medication related to LN or other immunosuppressive agents within 8 weeks prior to the endpoint 3. Initiation of prohibited medications at any time prior to the endpoint Note: adjustments in glucocorticoids are permitted up to and including Week 12. Nonsystemic glucocorticoids, NSAIDs, antimalarials and topical agents will not be considered an intercurrent event.	

Difference from Main Estimand: Participants with sustained increase of prednisone equivalent between Week 24 and Week 44 will not be allowed up to 40 mg/d for ≤10 days once for non-SLE/LN treatment (eg, COPD, asthma, contact dermatitis), and will not achieve CRR after the event.

5.4.2.2.7.4. Supplementary Estimand 3 for Time to Achievement of CRR through Week 52

All attributes (1-4) of the supplementary estimand are the same as above Main Estimand (Section 5.4.2.2.7.1) except for the intercurrent events, where the treatment policy strategy is omitted, and a composite strategy is added for participants not achieving CRR due to intercurrent events at Week 24 will also be non-achievers through Week 52.

5. Intercurrent events and their corresponding strategies:

Intercurrent Events	**Strategy for Addressing Intercurrent Events and Its Description**
Participants who do not achieve CRR due to intercurrent events at Week 24 will also be non-achievers through Week 52	**Composite Strategy:** A participant with this intercurrent event is considered to not have achieved CRR after this event, the occurrence of this intercurrent event being captured in the variable definition.
Discontinuation (DC) of study intervention for any reason excluding COVID-19 related discontinuations	**Composite Strategy:** Same as above
Medication Intercurrent Event	**Composite Strategy:** Same as above

4. Exceeding baseline glucocorticoid dose 5. Increase above 10 mg/d prednisone equivalent after Week 12, use of new or increased dose of concomitant medication related to LN or other immunosuppressive agents within 8 weeks prior to the endpoint 6. Initiation of prohibited medications at any time prior to the endpoint Note: adjustments in glucocorticoids are permitted up to and including Week 12. Nonsystemic glucocorticoids, NSAIDs, antimalarials and topical agents will not be considered an intercurrent event.	

Difference from main estimand: Participants who do not achieve CRR due to intercurrent events at Week 24 will also be non-achievers through Week 52. In addition, participants with sustained increase of prednisone equivalent between Week 24 and Week 44 will not be allowed up to 40 mg/d for ≤10 days once for non-SLE/LN treatment (eg, COPD, asthma, contact dermatitis), and will not achieve CRR after the event.

5.4.2.2.8. Time to treatment failure (TF)

Treatment Policy Estimand

1. Study intervention:

- Guselkumab (experimental treatment/intervention) in addition to standard-of-care
- Placebo in addition to standard-of-care

2. Population: Participants between 18 and 75 with active LN (defined by meeting the classification criteria for SLE by the 2019 European League Against Rheumatism (EULAR)/ACR, having a Class III-IV kidney biopsy documentation of ISN/RPS proliferative nephritis within the last 6 months prior to or during screening despite receiving one or more standard-of-care treatments.

3. Variable: Time to TF

4. Summary measure (Population-level summary): Hazard ratio of the guselkumab intervention group vs. the placebo intervention group

5. Intercurrent events and their corresponding strategies:

Intercurrent Events	Strategy for Addressing Intercurrent Events and Its Description
No intercurrent events for this endpoint	NA

5.4.2.3. Analysis Methods

Unless otherwise specified, the analysis population will be the FAS defined in Section 4. The endpoints will be summarized by study intervention groups.

Simple descriptive statistics, such as n, mean, SD, median, IQ range, minimum and maximum for continuous variables and counts and percentages for discrete variables will be used to summarize most data.

5.4.2.3.1. Binary Endpoints (Secondary Endpoints 1-6)

Analyses for binary secondary endpoints (proportion of response, improvement, reduction) will be based upon the estimands in Section 5.4.2.2.1 through Section 5.4.2.2.6.

Generalized linear model with logit link for a binary MMRM will be used to analyze the data for Secondary Endpoints 1 and 3-6 (main and supplementary). The model will include all available observed data after applying intercurrent events with treatment, visit, region, baseline UPCR level (<3 mg/mg and ≥3 mg/mg), and treatment and visit interaction in the model will be used to analyze the data. The 1-sided p-value from the difference in proportion of participants between the intervention groups will be provided. In addition, the estimate and its 80% CI estimated from the model will also be provided.

Logistic regression model will be used to analyze Secondary Endpoint 2 (main and supplementary). The model will include treatment, region, and baseline UPCR level (<3 mg/mg and ≥3 mg/mg). The 1-sided p-value, the odds ratio and the corresponding 80% CI between the intervention groups from the model will be provided.

5.4.2.3.2. Time to Event Endpoints (Secondary Endpoints 7-8)

Analyses for time to event endpoints will be based upon the estimands in Section 5.4.2.2.7 through Section 5.4.2.2.8.

The hazard ratio will be estimated using the Cox proportional hazards model, adjusting for region, baseline UPCR level (<3 mg/mg and ≥3 mg/mg), and its 80% CI will be calculated. The proportional hazards assumption will be verified with appropriate methods (e.g. log-minus-log plots) as part of the analysis. The reported p-values for time to first flare analyses will be derived from a log-rank test. The survival curves will be estimated using Kaplan-Meier estimates.

In general, point estimates and 80% CIs for comparison between treatment groups will be reported.

5.4.2.3.3. Sensitivity Analysis of the CRR endpoint using CRR-50% Pred definition

Secondary endpoints 1 and 4 will be analyzed using the same estimands as in Section 5.4.2.2.1 and 5.4.2.2.4. The difference is that the definition of CRR is replaced with CRR - 50% Pred (Section 5.4.2.1.2).

5.5. Tertiary/Exploratory Endpoint(s) Analysis

Early Termination Note: Due to the Sponsor's decision to stop screening of new participants as a result of enrollment challenges, fewer than 60 participants will be enrolled in the study. The end of study will occur after all enrolled participants have completed the Week 20 visit or discontinued study intervention prior to Week 24, and all participants have completed their final efficacy and safety visits per the SoA.

For the CSR, the analyses of tertiary/exploratory endpoints that are described in this section will not be performed.

Objective: To evaluate the efficacy of guselkumab in extrarenal lupus manifestations

The tertiary/exploratory endpoints to address the objective above are the following:

1. Proportion of participants with ≥4-point improvement at Week 24 in systemic lupus erythematosus disease activity index 2000 (SLEDAI-2K) modified to exclude renal items
2. Proportion of participants with baseline arthritis (with at least 4 active joints at baseline) who have ≥50% reduction in active joints at Week 24
3. Proportion of participants with baseline active mucocutaneous lupus manifestations (CLASI score ≥8) and ≥50% reduction in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) scores at Week 24

Objective: To evaluate the impact of guselkumab on Health-Related Quality of Life (HRQoL) and fatigue in participants with active LN

The tertiary/exploratory endpoints to address the objective above are the following:

4. Change from baseline in Lupus Quality of Life (LupusQoL) individual domains at Week 24
5. Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue score at Week 24
6. Change from baseline in lupus symptoms (joint pain, joint stiffness, rash, and swelling [peripheral edema]) at Week 24
7. Patient Global Impression of Change (PGIC) - Change in LN (health condition) at Week 24 and Week 52

Note: Other timepoints for these analyses will also be analyzed (Section 5.6).

5.5.1. Definition of Endpoint(s)

5.5.1.1. Four (4) Points Improvement from Baseline in SLE Disease Activity Index 2000 (SLEDAI-2K) Modified to Exclude Renal Items

The SLE disease activity index 2000 (SLEDAI-2K) is an established, validated SLE activity index. It is based on the presence of 24 features in 9 organ systems and measures disease activity in SLE patients in the previous 30 days; the index is weighted according to the feature. Features are scored by the assessing physician if present within the last 30 days, with more severe features having higher scores, and then simply added to determine the total SLEDAI-2K score, which ranges from 0 to 105 (Touma Z, et al, 2010; Touma Z, et al 2011b) The baseline measurement for the SLEDAI-2K is defined as the closest measurement taken prior to the initiation of the Week 0 study intervention administration.

SLEDAI improvement is defined as a reduction from baseline in total SLEDAI-2K score. No worsening of total SLEDAI-2K from baseline is defined as a change ≤0 in SLEDAI-2K score and meaningful improvement is best defined as a reduction in SLEDAI-2 K of 4 or more.

The SLEDAI-2K score will be calculated excluding the renal items (i.e., urinary casts, hematuria, proteinuria, pyuria).

5.5.1.2. Active Joints, Tender Joints, Swollen Joints

Assessment of active joints (defined as joints demonstrating tenderness and signs of inflammation), tender joints, and swollen joints will be performed at visits indicated in the SoA of the protocol. To be considered an active joint, an affected joint must demonstrate tenderness and at least one additional sign of inflammation (eg, observed swelling such as edema or effusion) on physical examination as determined by the joint assessor. Each of 28 joints will be evaluated for tenderness and swelling.

The joint assessment should be performed by an adequately trained joint assessor. Training on how the joint count will be performed will be provided by the Sponsor. An independent joint assessor would be preferred but if not available at the site, is not mandatory. It is strongly recommended that the same joint assessor perform these assessments at every visit. It is recommended that the designated assessor identify an appropriate back-up joint assessor in case the designated joint assessor is unavailable.

The arthritis score on the SLEDAI-2K should be in agreement with the active joint count assessment as calculated in the eCRF.

The endpoint is defined as a ≥50% reduction in active joints at Week 24 from baseline among participants with baseline arthritis (with at least 4 active joints at baseline).

5.5.1.3. Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) score

Cutaneous lupus disease activity and severity will be measured by the CLASI. The CLASI is an instrument to assess the disease activity and damage caused to the skin for cutaneous lupus

erythematosus (CLE) patients with or without systemic involvement (Albrecht J, et al, 2005). The CLASI consists of 2 scores; the first summarizes the activity of the disease while the second is a measure of the damage caused by the disease (CLASI Activity and CLASI Damage scores). Activity is scored by the Investigator based on erythema, scale/hyperkeratosis, mucous membrane involvement, acute hair loss, and non-scarring alopecia. Damage is scored in terms of dyspigmentation and scarring, including scarring alopecia. The scores are calculated by simple addition based on the extent of the symptoms (Albrecht J, et al, 2005).

- **CLASI scores** range from 0-70 for activity and 0-56 for damage, with higher scores indicating worse disease activity.

The endpoint is defined as a ≥50% reduction in CLASI score from baseline among participants with baseline active mucocutaneous lupus manifestations (CLASI ≥8). CLASI Activity and CLASI Damage will be analyzed independently.

5.5.1.4. Lupus Quality of Life Questionnaire

The LupusQoL questionnaire is a valid, lupus-specific HRQoL instrument consisting of 34 items across 8 domains (Physical health, Emotional health, Body image, Pain, Planning, Fatigue, Intimate relationships, and Burden to others) for self-administration. The final LupusQoL has a 5-point Likert response format, where 0=all the time, 1=most of the time, 2=a good bit of the time, 3=occasionally, and 4=never, and uses a 4-week recall period. The LupusQoL is scored by domain, with a higher score reflecting better HRQoL (McElhone K, et al, 2007).

5.5.1.5. FACIT-fatigue

The FACIT-fatigue version 4.0 is a 13-item questionnaire formatted for self-administration that assesses patient-reported fatigue and its impact upon daily activities and function over the past 7 days. Participants will be asked to answer each question using a 5-point Likert-type scale (0=Not at all; 1=A little bit; 2=Somewhat; 3=Quite a bit; and 4=Very Much). The interpretation of FACIT-fatigue scores is such that a higher score indicates less fatigue, with a range of possible scores of 0-52, with 0 being the worst possible score and 52 the best (FACIT, Lai J, et al, 2011)

Questions 1-6 and 9-13 are scored in reverse order. If 7 or more questions are answered, then the score can be calculated and is adjusted by the number of available questions.

5.5.1.6. Lupus Symptoms

Participants will be asked to report their worst severity of their joint pain, joint stiffness, skin rash, and swelling in legs and/or feet over the past 7 days on a 0 to 10 numeric rating scale, with the left anchor indicating “No [specific symptom]” and the right anchor, “Severe [specific symptom]”. The items are scored individually, with higher scores reflecting greater symptom severity. The administration frequency is described in the SoA of the protocol.

5.5.1.7. Patient Global Impression of Change

The PGIC in LN is a 1-item questionnaire based on the clinical global impressions assessment and is designed to assess a patient’s impression of the change in their health condition subsequent to receiving study treatment (Guy W, 1976). PGIC is a 7-point scale depicting a patient's rating of

overall change in their health condition following treatment. Patients rate their change in their LN since baseline by choosing one of the following response options: "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse." The PGIC will also serve as an anchor measure to explore clinically meaningful change thresholds for the other patient-reported outcome measures included in the study.

5.5.2. Analysis Methods

Unless otherwise specified, the analysis population will be the FAS defined in Section 4. The endpoints will be summarized by randomized study intervention groups.

Simple descriptive statistics, such as n, mean, SD, median, IQ range, minimum and maximum for continuous variables and counts and percentages for discrete variables will be used to summarize most data.

P-values provided for exploratory analyses will be nominal.

5.5.2.1. Binary Endpoints (Tertiary/Exploratory Endpoints 1-3)

Analyses for binary tertiary/exploratory endpoints (proportion of response, improvement, reduction) will be based upon the Composite Estimand (Section 5.4.2.2.3 for intercurrent events and strategies).

Generalized linear model with logit link for a binary MMRM will be used to analyze the data. The model will include all available observed data after applying intercurrent events with treatment, visit, region, baseline UPCR level (<3 mg/mg and ≥3 mg/mg), and treatment and visit interaction in the model will be used to analyze the data. The 1-sided p-value from the difference in proportion of participants between the intervention groups will be provided. In addition, the estimate and its 80% CI estimated from the model will also be provided.

5.5.2.2. Continuous Endpoints (Tertiary/Exploratory Endpoints 4-7)

Analyses for continuous endpoints will be based upon the Treatment Policy estimand.

The analysis will be performed using a MMRM based on observed data. The terms for this model are study intervention, region, baseline UPCR level (< 3 mg/mg, ≥ 3 mg/mg), baseline score, visit, and an interaction of treatment and visit. An unrestricted (UN) variance-covariance matrix for repeated measures within a participant will be used unless there are issues related to convergence, wherein an autoregressive matrix structure will be used instead. The 1-sided p-value from the difference between the intervention groups will be provided. In addition, the estimate and its 80% CI estimated from the model will also be provided.

5.6. Other Supportive Endpoints

Early Termination Note: Due to the Sponsor's decision to stop screening of new participants as a result of enrollment challenges, fewer than 60 participants will be enrolled in the study. The end of study will occur after all enrolled participants have completed the Week 20 visit or discontinued study intervention prior to Week 24, and all participants have completed their final efficacy and safety visits per the SoA.

For the CSR, the analyses of other supportive endpoints that are described in this section will not be performed.

In addition to the primary, secondary and tertiary/exploratory endpoints, other supportive efficacy analyses will be performed over time through Week 24 and 52.

Table 3 provides the list of supportive estimands and the respective analysis methods.

Table 3: Endpoints, Intercurrent Events Strategy and Analysis for Other Supportive Endpoints

	Endpoint	Intercurrent Event Strategy	Analysis (Section 5.6.1.1 and 5.6.1.2)	Endpoint Type
	Objective: To evaluate the efficacy of guselkumab in participants with active LN			
	Proportion of participants achieving at least 50% decrease in proteinuria from baseline over time	Treatment Policy	Binary MMRM	Binary
	Proportion of participants achieving complete renal response (CRR) over time	Treatment Policy	Binary MMRM	Binary
	Proportion of participants with Urine Protein to Creatinine Ratio (UPCR) <0.5 mg/mg over time	Treatment Policy	Binary MMRM	Binary
	Proportion of participants with UPCR <0.75 mg/mg over time	Treatment Policy	Binary MMRM	Binary
	Proportion of participants who achieve reduction in glucocorticoid dose by Week 12 and sustain that reduction through at least Week 24 or through Week 52 to ≤ 10 mg/day of prednisone or equivalent	Treatment Policy	Logistic regression	Binary
	Cumulative average daily glucocorticoid dose over time through Week 12, 24, 52	Treatment Policy	Summaries only	Continuous
	Objective: To evaluate the efficacy of guselkumab in extrarenal lupus manifestations			

	Proportion of participants with ≥4-point improvement in systemic lupus erythematosus disease activity index 2000 (SLEDAI-2K) modified to exclude renal items over time	Treatment Policy	Binary MMRM	Binary
	Change from baseline in (SLEDAI-2K) modified to exclude renal items over time	Treatment Policy	MMRM	Continuous
	Proportion of participants with baseline arthritis (with at least 4 active joints at baseline) who have ≥50% reduction in active joints over time	Treatment Policy	Binary MMRM	Binary
	Change from baseline in active, swollen and tender joints among participants with baseline arthritis (with at least 4 active joints at baseline) over time	Treatment Policy	MMRM	Continuous
	Proportion of participants with baseline active mucocutaneous lupus manifestations (CLASI score ≥8) and ≥50% reduction in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) scores over time	Treatment Policy	Binary MMRM	Binary
	Change from baseline in CLASI scores for participants with baseline active mucocutaneous lupus manifestations (CLASI score ≥8) over time	Treatment Policy	MMRM	Continuous
	Change from baseline in Physician's Global Assessment of Disease Activity (PGA) over time	Treatment Policy	MMRM	Continuous
	Objective: To evaluate the impact of guselkumab on HRQoL and fatigue in participants with active LN			
	Change from baseline in Lupus Quality of Life (LupusQoL) individual domains over time	Treatment Policy	MMRM	Continuous
	Proportion of participants who achieve minimum clinically important differences (MCID)	Treatment Policy	Binary MMRM	Binary

	cutoff of LupusQoL by domain over time			
	Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue score over time	Treatment Policy	MMRM	Continuous
	Proportion of participants Who Achieved ≥4-point Improvement from Baseline in FACIT-Fatigue over time	Treatment Policy	Binary MMRM	Binary
	Change from baseline in lupus symptoms (joint pain, joint stiffness, rash, and swelling [peripheral edema]) over time	Treatment Policy	MMRM	Continuous
	Patient Global Impression of Change (PGIC) - Change in LN (health condition) over time	Treatment Policy	MMRM	Continuous

5.6.1. Analysis Methods

Unless otherwise specified, the analysis population will be the FAS defined in Section 4. The endpoints will be summarized by study intervention groups.

Summaries over time will be for all visits data is collected through Week 52. Simple descriptive statistics, such as n, mean, SD, median, IQ range, minimum and maximum for continuous variables and counts and percentages for discrete variables will be used to summarize most data.

P-values provided for supportive analyses will be nominal.

5.6.1.1. Binary Endpoints

Analyses for binary secondary endpoints (proportion of response, improvement, reduction) will be based upon the Treatment Policy estimand.

- **Binary MMRM** - Generalized linear model with logit link for a binary MMRM will be used to analyze the data. The model will include all available observed data after applying intercurrent events with treatment, visit, region, baseline UPCR level (<3 mg/mg and ≥3 mg/mg), and treatment and visit interaction in the model will be used to analyze the data. The 1-sided p-value from the difference in proportion of participants between the intervention groups will be provided. In addition, the estimate and its 80% CI estimated from the model will also be provided.
- **Logistic regression -** A logistic regression model including treatment, region, and baseline UPCR level (<3 mg/mg and ≥3 mg/mg]) will be used to compare treatment groups. The 1-sided p-value, the odds ratio and the corresponding 80% Wald CI between intervention groups from the model will be provided.

5.6.1.2. Continuous Endpoints

Analyses for continuous endpoints will be based upon the Treatment Policy estimand.

MMRM - The analysis will be performed using a MMRM based on observed data. The terms for this model are study intervention, region, baseline UPCR level (<3 mg/mg, ≥3 mg/mg), baseline score, visit, and an interaction of treatment and visit. An unrestricted (UN) variance-covariance matrix for repeated measures within a participant will be used unless there are issues related to convergence, wherein an autoregressive matrix structure will be used instead. The 1-sided p-value from the difference between the intervention groups will be provided. In addition, the estimate and its 80% CI estimated from the model will also be provided.

5.7. Safety Analyses

Early Termination Note: Due to the Sponsor's decision to stop screening of new participants as a result of enrollment challenges, fewer than 60 participants will be enrolled in the study. The end of study will occur after all enrolled participants have completed the Week 20 visit or discontinued study intervention prior to Week 24, and all participants have completed their final efficacy and safety visits per the SoA.

For the CSR, all safety analyses described below will be performed on all available data through the end of study.

All safety analyses will be based on the safety analysis set based on actual intervention received, unless otherwise specified.

For all continuous safety variables, descriptive statistics by intervention group will include the N, mean, SD, median, minimum, and maximum. Categorical variables will be summarized by intervention group using frequency counts and percentages.

5.7.1. Extent of Exposure

The number and percentage of participants who receive IV or SC study interventions (guselkumab and placebo) will be summarized separately. The number and percentage of participants will also be summarized by visit.

Descriptive statistics for duration of study interventions (N, mean, SD, median, and range [minimum, maximum]) will be summarized. Participant-weeks of interventions are calculated as days of intervention/7. Participant-weeks will be presented by intervention group.

Study intervention duration is defined as (date of last dose of study intervention – date of first dose of study intervention) +1.

The number and percentage of participants with doses not administered will be summarized by intervention group. Reasons for doses not administered will also be summarized.

For IV and SC study intervention:

Descriptive statistics will be presented for the following parameters:

- Number of administrations
- Cumulative total dose

Study intervention compliance will be summarized descriptively. See Appendix 7 for further details.

5.7.2. Adverse Events

The verbatim terms used in the case report form by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention is considered to be treatment emergent. If the event occurs on the day of the initial administration of study intervention, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study intervention based on partial onset date or resolution date. All reported treatment-emergent AEs will be included in the analysis. For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

Summary tables and listings will be provided for treatment-emergent AEs:

- AEs
- Serious AEs (SAEs)
- AEs by severity, NCI-CTCAE toxicity grade
- AEs reasonably related to study intervention
- Had AEs leading to discontinuation of study intervention/termination of study participation

Summaries and listings of other treatment-emergent AEs of special interest will be provided. These include infections, serious infections, opportunistic infections, malignancies, hypersensitivity reactions, tuberculosis, AEs related to COVID-19, injection-site reactions, and AEs temporally associated with infusions.

Deaths will be displayed by actual study intervention received. A listing of study participants who died will be provided.

5.7.3. Additional Safety Assessments

5.7.3.1. Clinical Laboratory Tests

Clinical laboratory tests will be displayed for the participants included in the safety analysis set.

Descriptive statistics and graphical displays will be presented for selected chemistry and hematology, laboratory tests at scheduled time points.

Change from baseline through Week 24 and Week 52 will be summarized for chemistry and hematology tests and displayed by intervention group. A box plot of change from baseline through Week 24 and Week 52 will be provided.

- **Hematology assessments** will include but are not limited to the following: hemoglobin, hematocrit, platelet count, total and differential White Blood Cell count, B-cell analysis.
- **Blood chemistry assessments** will include but are not limited to the following: chemistry panel (total and direct bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, albumin, total protein, calcium, phosphate, sodium, potassium, chloride, blood urea nitrogen/urea, and creatinine).

The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 5.0) will be used in the summary of laboratory data (Grade 0-4). The proportion of participants with post-baseline values by maximum toxicity grade for clinical laboratory tests will be summarized by study intervention group. Participants with toxicity grades ≥ 2 will be listed.

5.7.3.2. Electronic Columbia-Suicide Severity Rating Scale

The Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) will be used as a screening tool to prospectively evaluate suicidal ideation and behavior among study participants. The eC-SSRS measures 5 possible levels of suicidal ideation and 4 possible suicidal behaviors, as well as non-suicidal self-injurious behavior. The assessment is a fully-structured, participant self-report eC-SSRS questionnaire, including standardized questions, follow-up prompts, error handling routines, and scoring conventions (Mundt JC, et al, 2013; Posner K, et al, 2011). Two versions of the eC-SSRS will be used in this study, the *Lifetime* version and the *Since Last Contact* version. The *Lifetime* version will be conducted during the screening visit and the *Since Last Contact* version will be conducted at all other visits.

At the conclusion of each assessment, the eC-SSRS Findings Report can be viewed electronically. At screening ("In the last 6 months") and Week 0, participants with an Ideation level (1-5) or any suicidal behaviors or with a response of "YES" for non-suicidal, self-injurious behavior must be determined to be not at risk by the investigator based on an evaluation by a mental health professional in order to be randomized. Participants with an Ideation level (1-5) on the eC-SSRS or any suicidal behaviors or with a response of "YES" for non-suicidal, self-injurious behavior at any postbaseline visit will also be referred to an appropriate mental health professional for evaluation. If a participant's psychiatric disorder can be adequately treated with psychotherapy and/or pharmacotherapy then the participant, at the discretion of the investigator, should be continued with treatment. Ultimately, the determination of suicidality and risk is up to the investigator's clinical judgment following evaluation by a mental health professional (eg, psychiatrist, psychologist, or appropriately trained social worker or nurse).

The eC-SSRS Findings Report will be summarized by intervention group for each finding: Ideation 1-5, and Behaviors (Actual (non-fatal and completed), Interrupted, Aborted and Preparatory attempts).

5.7.3.3. Vital Signs and Physical Examination Findings

Continuous vital sign parameters including weight, height, pulse, and blood pressure (systolic and diastolic) will be summarized at each assessment time point. Change from baseline of the vital sign parameters will be summarized for through Week 24 and through Week 60. Descriptive statistics (mean, SD, median, minimum and maximum) will be presented.

Summaries of treatment-emergent abnormal vital signs during intervention, as defined in Table 4, will be provided for participants who had a baseline assessment and at least 1 postbaseline assessment for that vital sign. A listing of participants with treatment-emergent abnormal vital signs will be presented.

Table 4: Abnormal Vital Sign Parameters

Vital Sign	Criteria
Pulse	>130 bpm or <50
Systolic blood pressure	>180 mm Hg or <85 mm Hg
Diastolic blood pressure	>115 mm Hg or <55 mm Hg
Weight	Increase/decrease 10 kg from baseline

5.8. Other Analyses

Early Termination Note: Due to the Sponsor's decision to stop screening of new participants as a result of enrollment challenges, fewer than 60 participants will be enrolled in the study. The end of study will occur after all enrolled participants have completed the Week 20 visit or discontinued study intervention prior to Week 24, and all participants have completed their final efficacy and safety visits per the SoA.

For the CSR, PK Active Study Intervention serum concentration over time will be summarized and displayed graphically. Antibodies to guselkumab status over time will be summarized and a listing of participants positive for antibodies to guselkumab may be presented when appropriate. All other analyses that are specified in this section will not be reported in the CSR.

5.8.1. Pharmacokinetics

PK analyses will be performed on the PK analysis set, defined as participants who have received at least 1 dose of Active Study Intervention and have at least 1 post initial dose blood sample drawn for PK analysis.

If anti-Active Study Intervention antibodies are detected in certain participants, PK parameters may be summarized with and without these participants.

Descriptive statistics (N, mean, SD, median, range, and IQ range) will be used to summarize Active Study Intervention/Analyte serum concentrations at each sampling time point. PK data will be displayed graphically, such as mean +/- SD PK concentrations over time by intervention group.

Active Study Intervention concentrations below the lower limit of quantification×minimum required dilution will be imputed as zero in the summary statistics.

Active Study Intervention concentrations will be presented based on baseline body weight quartiles at each time point.

PK data may be displayed graphically, such as mean +/- SD PK concentrations over time by weight group.

If sufficient data are available, then population PK analysis using serum concentration-time data of Active Study Intervention will be performed using nonlinear mixed-effects modeling. Details will be given in a population PK analysis plan and the results of the analysis will be presented in a separate report.

Urine/PK concentration will be summarized in a separate report.

5.8.2. Immunogenicity

"Sample ADA status" and sample titer as well as the cumulative "participant ADA status" and peak titer through the visit will be coded and provided by the bioanalytical group.

Participants evaluable for immunogenicity are defined as having at least one postdose anti-drug antibody (ADA) time point collected for anti-guselkumab antibody detection.

Participants with treatment-emergent anti-guselkumab antibodies include participants with treatment-induced anti-guselkumab antibodies and treatment-boosted anti-guselkumab antibodies.

Participants with treatment-induced anti-guselkumab antibodies have an anti-guselkumab antibodies negative sample prior to guselkumab administration and at least one anti-guselkumab antibodies positive sample after guselkumab.

Participants with treatment-boosted anti-guselkumab antibodies have an anti-guselkumab antibodies positive sample prior to guselkumab administration and at least one anti-guselkumab antibodies positive sample after guselkumab with a [2]-fold increase in titer over baseline.

In participants who have a positive sample prior to guselkumab administration, if titer remains the same after intervention or if ADA titer reduces or ADA disappears, the participant is classified as "treatment-emergent ADA negative". Participants that are unavailable for treatment-emergent ADA following intervention will be classified as "participants with baseline samples only", ie, no appropriate sample is available after intervention.

The anti-guselkumab antibodies summary and analysis will be based on the observed data; therefore no imputation of missing data will be performed. Note: participant status is through each visit, thus, participant status and peak titers may change as the study progresses over time. Therefore, the 'participant ADA status' at a visit represents the cumulative ADA status through that visit. For example, if a study has a lock at Week 24, datasets through Week 24 will have participant level status (eg, negative) but at Week 52, they may have developed ADA and the

participant status becomes "treatment-emergent ADA positive" from the interim to the final DBL. Peak titers can also change (increase) if a higher titer occurs after an initial DBL.

The summary of participants with baseline positive samples is taken from the sample status at baseline. There is no participant level status at baseline.

Incidence of antibody (evaluable, treatment-emergent ADA positive, treatment-emergent ADA negative) status and neutralizing antibodies to guselkumab will be summarized by intervention group.

In addition, listings of participants with baseline positive ADA samples, participants who are classified as positive for treatment-emergent anti-guselkumab antibodies and participants who discontinue the study by anti-guselkumab antibodies status as well as graphical representation of median serum guselkumab concentration by antibody status may be presented.

The Peak Titer for participants positive for treatment-emergent anti-guselkumab antibodies will be grouped by Peak Titer categories. Example: <=1:10, 10 to 100, 100 to 1000, >1000, if needed.

Incidence of treatment-emergent positive antibody across Peak Titer categories might be summarized.

Descriptive statistics (N, mean, SD, median, range, and IQ range) and incidence (N, %) of the relationship between treatment-emergent anti-guselkumab antibodies status (positive or negative) and PK concentration will be assessed.

Participants in response (N, %) for treatment-emergent anti-guselkumab antibodies status (positive or negative) and efficacy endpoints will be assessed:

- Participants evaluable for immunogenicity
- Efficacy endpoints repeated for different levels of response (eg, proportion of participants achieving at least 50% decrease in proteinuria from baseline at Week 24, proportion of participants achieving complete renal response (CRR) at Week 52 and change in UPCR)
  - Number of participants (N)
    - Participants in response (N, %)

Incidence (N, %) between treatment-emergent anti-guselkumab antibodies status (positive or negative) and infusion-related reactions will be assessed:

- Participants evaluable for immunogenicity
- Participants with infusion-related reaction
- Participants with severe infusion-related reaction
- Participants with serious infusion-related reaction
- Participants with infusion-related reaction leading to discontinuation

- Guselkumab infusions with infusion-related reactions (out of total number of guselkumab infusions)
- Placebo infusions with infusion-related reactions (out of total number of placebo infusions).

Incidence (N, %) between treatment-emergent anti-guselkumab antibodies status (positive or negative) and injection site reactions will be assessed:

- Participants evaluable for immunogenicity
- Participants with injection site reaction
- Participants with severe injection site reaction
- Participants with serious injection site reaction
- Participants with injection site reaction leading to discontinuation
- Guselkumab injections with injection site reactions (out of total number of guselkumab injections)
- Placebo injections with injection site reactions (out of total number of placebo injections).

5.8.3. Pharmacodynamics / Biomarker Analyses

Changes in the concentration and proportion of subjects with abnormalities of individual pharmacodynamic biomarkers from baseline to the selected post treatment time points will be summarized. These include but are not limited to antinuclear antibody, anti-phospholipid antibodies, anti-ds-DNA, C3 and C4 complement, Cystatin C, IgA, IgG, and IgM.

It should be noted that a separate pharmacodynamics / biomarker report will be produced and associated analyses of serum, cellular and whole blood gene expression will be reported in that document.

5.8.4. Pharmacokinetic/Pharmacodynamic Relationships

If deemed feasible and necessary, exposure-response analyses may be performed. The analysis methods may be summarized in a separate analysis plan. Results of such analyses may be presented in a separate technical report.

5.8.5. Definition of Subgroups

To evaluate the consistency of the primary efficacy endpoint (proportion of participants with achieving at least 50% decrease in proteinuria from baseline at Week 24) subgroup analyses may be performed when the number of participants in the subset permits (at least 5 participants for each treatment group within a subset).

The subgroups for subgroup analysis may include, but are not limited to, the following:

1. Demographic subgroups

Subgroup	Variant	Definition
Region	1	Define based on UN guidance as per the M49 standard • Asia Pacific • North America • Latin America • Europe
Age Group	1	• <55 • ≥55
Body Mass Index (BMI)	1	• normal <25 kg/m^2 • overweight 25-<30 kg/m^2 • obese >=30 kg/m^2
Body Weight Group	1 (Quartiles)	•
Race	1	• White • Black • Asian • All other categories
Ethnicity	1	• Hispanic or Latino • Not Hispanic or Latino
Gender	1	• Male • Female
Participants age at LN diagnosis	1	• < 21 years • ≥ 21 years

2. Disease Characteristics subgroups

Subgroup	Variant	Definition
Renal biopsy classes		• III • III + V • IV • IV + V
Nephrotic proteinuria defined as urine P/C ratio of >=3	1	• UPCR <3 • UPCR ≥3
	2	• < Median • ≥ Median
eGFR		• eGFR ≥ 90 • eGFR ≥ 60 and < 90 • eGFR ≥ 30 and < 60 • eGFR < 30
SLEDAI-2K Score		• < Median • ≥ Median
PGA Score		• < Median • ≥ Median
Serologic status individually and collectively for anti-dsDNA, C3 and C4		

Subgroup	Variant	Definition
(i) dsDNA (positive, negative)		• Positive • Negative
(ii) Complement C3, C4		• Normal • Abnormal

3. Prior Medication subgroups

Subgroup	Variant	Definition
Glucocorticoids only		Yes or No
Glucocorticoids + Antimalarials		Yes or No
Glucocorticoids + Immunosuppressants		Yes or No
Glucocorticoids + Ace-inhibitors		Yes or No
Antimalarials + Immunosuppressants		Yes or No
Antimalarials + Ace-inhibitors		Yes or No
Immunosuppressants + Ace-inhibitors		Yes or No
Glucocorticoids + Antimalarials + Immunosuppressants		Yes or No
Glucocorticoids + Antimalarials + Ace-inhibitors		Yes or No
Antimalarials + Immunosuppressants + Ace-inhibitors		Yes or No
Glucocorticoids + Antimalarials + Immunosuppressants + Ace-inhibitors		Yes or No

5.9. Interim Evaluations

Early Termination Note: Due to the Sponsor's decision to stop screening of new participants as a result of enrollment challenges, fewer than 60 participants will be enrolled in the study. The end of study will occur after all enrolled participants have completed the Week 20 visit or discontinued study intervention prior to Week 24, and all participants have completed their final efficacy and safety visits per the SoA.

The first interim efficacy evaluation occurred on December 28, 2021. Due to early termination of the study, the second and third interim efficacy evaluations will not be performed.

Details of the Data Monitoring Committee (DMC) safety reviews and interim analysis assessments are included in a separate DMC Charter and DMC SAP. The DMC SAP contains definitions of analysis sets, derived variables, scope and objects of the DMC, data-cutoff points, statistical methods and output to be produced for the safety reviews and evaluation of efficacy as required by the DMC Charter. Additionally, a dedicated DMC Data Presentation Specifications (DPS) document details output and programming specifications.

The follow offers a high-level summary of the DMC activities.

5.9.1. Interim Efficacy Evaluations

Three interim efficacy evaluations will be conducted, when approximately 10, 25 and 40 participants respectively complete the Week 24 visit. The first interim efficacy evaluation is contingent to occur prior to the first participant entering the long-term extension, based on enrollment, that is when ~10 participants complete the Week 24 visit.

It should be noted that the first interim efficacy evaluation will occur 2 months prior to the first patient entering the LTE. It is projected that at that time, ~10 participants will complete the Week 24 visit. If enrollment is expedited and as many as ~25 patients reach the Week 24 visit instead, then the first and second interim efficacy evaluations will be combined. Otherwise, the first and second interim efficacy evaluation will occur separately. This decision to combine the first and second interim efficacy evaluation will be made ~4 months prior to the first patient entering LTE.

The DMC will review the unblinded efficacy data and make observations about the next step of study/program conduct, based upon the results of the interim efficacy evaluations.

The primary endpoint will be used for the interim efficacy evaluations.

A Bayesian predictive analysis based on a beta-binomial distribution on longitudinal data will be used for the analysis at each evaluation. At each of the three interim efficacy evaluations, if the predictive probability of success at the end of the study (the 1-sided p-value from the difference in proportion of participants with ≥50% decrease in proteinuria between the guselkumab and placebo intervention groups is less than a 1-sided alpha of 10%), given the current results, is <10% then the futility criteria would be met.

5.9.1.1. First Interim Efficacy Evaluation

At the first interim efficacy evaluation meeting (prior to the first participant entering the long-term extension, when approximately 10 participants complete their Week 24 visit), the DMC will examine efficacy for futility of advancing to the long-term extension based upon the predictive probability of success of the study given the available data up to Week 24 at that point. The possible recommendations of the DMC concerning efficacy at the first meeting include:

1. **Criteria for evidence for futility was met.** If the futility criterion is met, the DMC will recommend not advancing to the long-term extension of the study.
2. **Criteria for evidence of futility was NOT met.** If the futility criterion is not met, the DMC will recommend the participants that qualify continue to advance to the long-term extension of the study.

5.9.1.2. Second and Third Interim Efficacy Evaluation

At the second and third DMC interim efficacy evaluation (when approximately 25 and 40 participants, respectively, complete their Week 24 visit), the DMC will examine efficacy for futility based on the predictive probability of success given the available data up to Week 24 at that point. The possible observations of the DMC concerning efficacy at the second and third meeting include:

1. **Criteria for evidence of futility was met.** If the futility criterion is met, the DMC will recommend to stop the study. Furthermore, the DMC will recommend to stop enrollment of additional participants due to futility if all planned participants have not been enrolled.

2. **Criteria for evidence of futility was not met.** If the futility criterion is not met, the DMC will recommend continuing the study.

Details are outlined in the DMC SAP.

5.9.2. Data Monitoring Committee

The independent DMC will monitor data on an ongoing basis to ensure the continuing safety of the participants enrolled in the study. The committee will meet periodically to review interim data. After the review, the DMC will make recommendations regarding the continuation of the study. Any safety concerns will be communicated to the Sponsor Committee Chairperson.

None of the DMC members will be participating in the study; they will be independent of the Sponsor. The independent DMC consists of 2 medical experts in relevant therapeutic areas and 1 statistician and are to be specified before study initiation. The major function of the DMC is to monitor the safety of the study intervention, to evaluate efficacy data and provide recommendations for placing the study on hold or stopping the study in the event of serious safety concerns or futility.

Periodic safety reviews will occur as outlined in the DMC Charter, initiating when the 5th participant has been randomized or 3 months after the first participant is dosed, whichever comes first. Subsequent meetings will occur approximately every 4 months until the last meeting which will be within 6 months of the Week 60 DBL.

Serious adverse events will be reported to the DMC members on an ongoing basis. The DMC will have access to the unblinded data and review tabulated safety summaries (if appropriate) and any additional safety data that the DMC may request.

The content of the safety summaries and interim efficacy evaluations, the DMC roles and responsibilities and the general procedures (including communication plan) and their possible recommendations on study conduct will be defined and documented in the DMC Charter prior to the first DMC review.

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APPENDICES

APPENDIX 1: LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ADA	anti-drug antibody
AE	adverse event
ANCOVA	analysis of covariance
Anti-dsDNA	anti-double stranded deoxyribonucleic acid
ATC	anatomic and therapeutic class
BMI	body mass index
CI	confidence interval
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CMH	Cochran-Mantel-Haenszel
Cx	Complementx (eg, C3)
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRR	Complete Renal Response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DBL	database lock
DC	discontinuation
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
eCRF	electronic case report form
eC-SSRS	Electronic Columbia-Suicide Severity Rating Scale
eGFR	Estimated Glomerular Filtration Rate
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy Fatigue
FAS	full analysis set
HRQoL	Health-Related Quality of Life
IL-xx	Interleukin-xx (eg. IL-23)
IQ	interquartile
ISN/RPS	International Society of Nephrology and Renal Pathology Society
IV	intravenous
Kg	kilogram
LLN	lower limit of normal
LN	lupus nephritis
LTE	long-term extension
LupusQoL	Lupus Quality of Life
m^2	meter squared
MCID	minimum clinically important differences
MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligram
MI	multiple imputation
MMF	mycophenolate mofetil
MMRM	mixed effects repeated measures model
MPA	mycophenolic acid
NSAIDs	nonsteroidal anti-inflammatory drug
PBMC	peripheral blood mononuclear cell

PD	pharmacodynamic(s)
PGA	Physician's Global Assessment of Disease Activity
PGIC	Patient Global Impression of Change
PK	pharmacokinetic(s)
q4w	every 4 weeks
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
SLE	systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SoA	Schedule of Activities
TF	treatment failure
ULN	upper limit of normal
UPCR	Urine Protein Creatinine Ratio
V	volume distribution
WBC	white blood cell
WHO-DD	World Health Organization Drug Dictionary

APPENDIX 2: CHANGES TO PROTOCOL-PLANNED ANALYSES

N/A

APPENDIX 3: DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The number of participants in each analysis set will be summarized and listed by intervention group, and overall. In addition, the distribution of participants by region, country, and site ID will be presented unless otherwise noted.

Table 5 presents a list of the demographic variables that will be summarized by intervention group, and overall for the FAS analysis set(s). Demographics will also be summarized by region using the FAS analysis set. Table 6 presents the baseline disease characteristics variables that will be summarized by intervention group and overall for the FAS analysis set(s).

Table 5: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m^2)	
Categorical Variables	
Age <55 years, and >=55 years])	Frequency distribution with the number and percentage of participants in each category.
Sex (male, female)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
BMI ([normal <25 kg/m^2, overweight >=25 kg/m^2])	

Table 6: Baseline Disease Characteristics Variables

Continuous Variables:	**Categories**	**Summary Type**
Proteinuria (urine P/C ratio) (mg/mg)		Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
eGFR (mL/min/m^2)		
SLEDAI-2K score (0-105)		
PGA score (0-3)		
Active joints with both pain and inflammation (0-28)		
Number of joints with pain (only) (0-28)		
Number of joints with swelling (only) (0-28)		
CLASI Damage Score (0-56)		
CLASI Activity Score (0-70)		
Lupus Quality of Life (LupusQOL) score and individual domains		
FACIT-Fatigue score		
Lupus Symptoms:		
Joint pain scale (0-10)		
Joint stiffness scale (0-10)		
Rash scale (0-10)		
Swelling scale (0-10)		
LN duration		
SLE duration		
Categorical Variables		Frequency distribution with the number and percentage of participants in each category.
LN Flare	• Yes • No	
Renal biopsy classes	• III • III + V • IV • IV + V	
Nephrotic proteinuria defined as urine P/C ratio of >=3	• UPCR <3 • UPCR ≥3	
eGFR	• eGFR ≥ 90 • eGFR ≥ 60 and < 90 • eGFR ≥ 30 and < 60 • eGFR < 30	
dsDNA (positive, negative)	• Positive • Negative	
Complement C3, C4	• Normal • Abnormal	

APPENDIX 4: PROTOCOL DEVIATIONS

In general, the following list of major protocol deviations may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to DBL and the participants with major protocol deviations will be summarized by category.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other
    - Missed visit/assessment due to COVID-19

APPENDIX 5: PRIOR AND CONCOMITANT MEDICATIONS

Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study intervention. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study intervention, including those that started before and continue on after the first dose of study intervention.

Summaries of concomitant medications will be presented by anatomic and therapeutic class (ATC) term, and intervention group. The proportion of participants who receive each concomitant medication will be summarized as well as the proportion of participants who receive at least 1 concomitant medication. In addition, concomitant medications of special interest will be presented.

Prior medications will be summarized by intervention group and ATC term.

APPENDIX 6: MEDICAL HISTORY

Medical history of lupus and body system will be listed and summarized by intervention groups.

APPENDIX 7: INTERVENTION COMPLIANCE

Compliance will be summarized descriptively for each study intervention. Compliance to randomized intervention versus actual intervention will be presented in a summary table.

APPENDIX 8: ADVERSE EVENTS OF SPECIAL INTEREST

N/A

APPENDIX 9: MEDICATIONS OF SPECIAL INTEREST

N/A

APPENDIX 10: LABORATORY TOXICITY GRADING

The grading scale used for lab assessments is based on 'Common Terminology Criteria for Adverse Events (CTCAE) v5.0'.

If a laboratory value falls within the grading as specified below but also within the local laboratory normal limits, the value is considered to be normal and will be reset to grade 0.

Pre-baseline measurements will use the same grading ranges as applied to baseline measurements. In case a test has two sets of ranges – one for baseline normal and one for baseline abnormal, the one for baseline normal will be applied for all measurements taken pre-baseline and on baseline.

Text in gray italic in the table is present in the grading scale, but is not applied by Janssen when grading lab data.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Blood and lymphatic system disorders					
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hemoglobin (Hgb) <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hemoglobin (Hgb) <8.0 g/dL; <4.9 mmol/L; <80 g/L; *transfusion indicated*	*Life-threatening consequences; urgent intervention indicated*	Clinical signs and symptoms are not taken into consideration for grading.
Leukocytosis	-	-	>100,000/mm3; >100 x 10e9 /L	*Clinical manifestations of leucostasis; urgent intervention indicated*	Clinical signs and symptoms are not taken into consideration for grading; Added ranges in SI unit (x 10e9 /L)
Investigations					
Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; *bleeding*	-	Clinical signs and symptoms are not taken into consideration for grading.
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
CD4 lymphocytes decreased	<LLN - 500/mm3; <LLN - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200 - 50/mm3; <0.2 x 0.05 - 10e9 /L	<50/mm3; <0.05 x 10e9 /L	
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	
Creatinine increased	Creatine Kinase >ULN - 1.5 x ULN	Creatine Kinase >1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	Creatine Kinase >3.0 x baseline; >3.0 - 6.0 x ULN	Creatine Kinase >6.0 x ULN	
Fibrinogen decreased	<1.0 - 0.75 x LLN; if abnormal, <25% decrease from baseline	<0.75 - 0.5 x LLN; if abnormal, 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN; if abnormal, 50 - <75% decrease from baseline	<0.25 x LLN; if abnormal, 75% decrease from baseline; absolute value <50 mg/dL	Ranges defined for "abnormal" are applied only on values < LLN. Grade 0 will be assigned to values > ULN.
GGT increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Haptoglobin decreased	<LLN	-	-	-	
Hemoglobin increased	Increase in >0 - 2 g/dL; Increase in >0 - 20 g/L	Increase in >2 - 4 g/dL; Increase in >20 - 40 g/L	Increase in >4 g/dL; Increase in >40 g/L	-	The increase indicates the level of increase above normal (above ULN). Applied as, e.g. grade 1 (g/dL): >ULN – ULN+2 g/dL; Added ranges in SI unit (g/L).

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
INR increased	>1.2 - 1.5; *>1 - 1.5 x baseline if on anticoagulation; monitoring only indicated*	>1.5 - 2.5; *>1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated*	>2.5; *>2.5 x baseline if on anticoagulation; bleeding*	-	Concomitant therapy or clinical signs and symptoms are not taken into consideration for grading.
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; *>2.0 - 5.0 x ULN and asymptomatic*	>2.0 - 5.0 x ULN with signs or symptoms; *>5.0 x ULN and asymptomatic*	>5.0 x ULN and with signs or symptoms	"Asymptomatic" ranges are not taken into consideration for grading, i.e. worst case grading is applied.
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3; >4 - 20 x 10e9 /L	>20,000/mm3; >20 x 10e9 /L	-	Added ranges in SI unit (x 10e9 /L).
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	Both Neutrophils and segmented neutrophils are graded using these criteria.
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; *>2.0 - 5.0 x ULN and asymptomatic*	>2.0 - 5.0 x ULN *with signs or symptoms; >5.0 x ULN and asymptomatic*	>5.0 x ULN *and with signs or symptoms*	"Asymptomatic" ranges are not taken into consideration for grading, i.e. worst case grading is applied.
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	
Metabolism and nutrition disorders					
Acidosis	pH <normal, but >=7.3	-	pH <7.3	*Life-threatening consequences*	pH <normal is implemented as pH <LLN. Clinical signs and symptoms are not taken into consideration for grading.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Alkalosis	pH >normal, but <=7.5	-	pH >7.5	*Life-threatening consequences*	pH >normal is implemented as pH >ULN. Clinical signs and symptoms are not taken into consideration for grading.
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; *symptomatic*	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; *hospitalization indicated*	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hyperkalemia	Potassium >ULN - 5.5 mmol/L	Potassium >5.5 - 6.0 mmol/L; *intervention initiated*	Potassium >6.0 - 7.0 mmol/L; *hospitalization indicated*	Potassium >7.0 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypermagnesemia	Magnesium >ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	Magnesium >3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	Magnesium >8.0 mg/dL; >3.30 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypernatremia	Sodium >ULN - 150 mmol/L	Sodium >150 - 155 mmol/L; *intervention initiated*	Sodium >155 - 160 mmol/L; *hospitalization indicated*	Sodium >160 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypertriglyceridemia	Triglycerides 150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	Triglycerides >300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	Triglycerides >500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	Triglycerides >1000 mg/dL; >11.4 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypoalbuminemia	Albumin <LLN - 3 g/dL; <LLN - 30 g/L	Albumin <3 - 2 g/dL; <30 - 20 g/L	Albumin <2 g/dL; <20 g/L	*Life-threatening consequences; urgent intervention indicated*	Clinical signs and symptoms are not taken into consideration for grading.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; *symptomatic*	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; *hospitalization indicated*	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypoglycemia	Glucose <LLN - 55 mg/dL; <LLN - 3.0 mmol/L	Glucose <55 - 40 mg/dL; <3.0 - 2.2 mmol/L	Glucose <40 - 30 mg/dL; <2.2 - 1.7 mmol/L	Glucose <30 mg/dL; <1.7 mmol/L; *life-threatening consequences; seizures*	Clinical signs and symptoms are not taken into consideration for grading. Urine glucose is not graded.
Hypokalemia	*Potassium <LLN - 3.0 mmol/L*	*Symptomatic with* Potassium <LLN - 3.0 mmol/L; intervention indicated	Potassium <3.0 - 2.5 mmol/L; *hospitalization indicated*	Potassium <2.5 mmol/L; *life-threatening consequences*	"Symptomatic" ranges are applied for grade 2, grade 1 not assigned, i.e. worst case applied. Clinical signs and symptoms are not taken into consideration for grading of grade 3 and 4.
Hypomagnesemia	Magnesium <LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	Magnesium <1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	Magnesium <0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	Magnesium <0.7 mg/dL; <0.3 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Hyponatremia	Sodium <LLN - 130 mmol/L	*Sodium 125-129 mmol/L and asymptomatic*	*Sodium 125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms* Sodium <130-120 mmol/L	Sodium <120 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading. Worst case ("<130-120 mmol/L" for grade 3 added by Janssen) is applied across grade 2/3 ranges: 120-129 mol/L assigned to grade 3, grade 2 not used.

* Grade 0 is assigned to a lab assessment when the lab test is described in the table, but the lab value is not assigned a grade 1 or higher.