Janssen Research & Development *

Clinical Protocol

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

ORCHID-LN

Short Title
A Study of the Efficacy and Safety of Guselkumab in Participants with Active Lupus Nephritis

Protocol CNTO1959LUN2001; Phase 2
Amendment 4
CNTO 1959 (guselkumab)

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United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

Regulatory Agency Identifier Number(s):
IND: p140547
EudraCT NUMBER: 2018-003155-38

Status:	Approved
Date:	24 May 2022
Prepared by:	Janssen Research & Development, LLC
EDMS number:	EDMS-ERI-166768011, 5.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 4	24 May 2022
Amendment 3	29 March 2022
Amendment 2	20 May 2021
Amendment 1	07 May 2020
Original Protocol	18 February 2020

Amendment 4 [24 May 2022]

Overall Rationale for the Amendment: To revise the protocol to reflect the sponsor's decision to stop screening of new participants and terminate the study early, as a result of enrollment challenges.

The changes made to the clinical protocol CNTO1959LUN2001 as part of Protocol Amendment 4 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.13 Appendix 13.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis; 3 Objectives and Endpoints.	Added text that not all Objectives and Endpoints described may be reported in the CSR.	Due to enrollment challenges, the sponsor made the decision to stop screening of new participants and terminate the study early. The changes in this amendment describe study conduct for currently screened and randomized participants in the context of the plan for early study termination.
1.1 Synopsis; 9 Statistical Considerations.	Added text that not all statistical analyses described may be performed.	
1.1 Synopsis; 4.1 Overall Design; 6.3 Measures to Minimize Bias: Randomization and Blinding.	Updated details for planned database locks.	
1.1 Synopsis; 2.1 Study Rationale; 4.1.1 Main Study; 7.1 Discontinuation of Study Intervention; 9.2 Sample Size Determination.	Updated details of number of participants to be enrolled in the study.	
9.3 Populations for Analysis Sets.	Defined additional populations for analysis.	
1.1 Synopsis; 4.1.2 Long-Term Extension; 6.1.1 Long-Term Extension; 6.3 Measures to Minimize Bias: Randomization and Blinding.	Updated information regarding blinding during the study.	
1.3 Schedule of Activities (SoA).	Defined the timing for final efficacy and safety visits for participants prior to, and after, early study termination notification.	
1.1 Synopsis; 4.1 Overall Design; 4.4 End of Study Definition; 6.1 Study Interventions Administered; 6.1.1 Long-Term Extension.	Defined the end of study.	

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis; 4.1 Overall Design.	Updated information regarding study termination and administration of study intervention.	
1.1 Synopsis; 4.1.2 Long-Term Extension; 6.1.1 Long-term Extension; 9.4.8 Long-Term Extension.	Updated description of end of LTE.	
5.4 Screen Failures.	Updated information regarding rescreening of participants.	
6.3 Measures to Minimize Bias: Randomization and Blinding.	Specified when randomization codes will be disclosed fully.	
3 Objectives and Endpoints.	Corrected the units for eGFR in the CRR definition.	Corrected typo.
Throughout the protocol.	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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1. PROTOCOL SUMMARY

1.1. Synopsis

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

Guselkumab (CNTO 1959) is a fully human immunoglobulin G1 lambda monoclonal antibody (mAb) that binds to human interleukin (IL)-23 with high affinity. The binding of guselkumab to IL-23 blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23-specific intracellular signaling and subsequent activation and cytokine production. In this manner, guselkumab inhibits the biological activity of IL-23 in all in vitro assays examined.

EudraCT Number: 2018-003155-38

IND Number: p140547

OBJECTIVES AND ENDPOINTS

Due to the Sponsor's decision to terminate the study early, only the primary endpoint, major secondary endpoints and safety endpoints may be reported in the clinical study report. Details will be described in the statistical analysis plan (SAP).

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 • **Major 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 • 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,

Objectives	Endpoints
	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 pharmacokinetics (PK) and immunogenicity in participants with active LN	• Serum guselkumab levels over time • Serum anti-guselkumab antibodies through Week 24, through Week 60, end of long-term extension (LTE), and in participants discontinuing study intervention early
Tertiary/Exploratory	
• To evaluate the efficacy of guselkumab in participants with active LN over an extended period	• Proportion of participants maintaining CRR at Week 152
• To evaluate the efficacy of guselkumab in extrarenal lupus manifestations	• Proportion of participants with ≥4 points 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 (Cutaneous Lupus Erythematosus Disease Area and Severity Index [CLASI] score ≥8) and ≥50% reduction in 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 • Changes in PRO assessments including LupusQOL, FACIT-Fatigue, lupus symptoms, and PGIC over time during the long-term extension
• To evaluate biomarkers of LN, pharmacodynamic (PD) effects of guselkumab, and to identify participants most likely to	• Serum biomarkers including IL-23, IL-17A, IL-17F, IL-22, complement (C)3, C4, C1q, or autoantibodies, eg, anti-double-stranded deoxyribonucleic acid (dsDNA)

Objectives	Endpoints
benefit from treatment with guselkumab	• 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 [IFN]-gamma, chemokines), and/or tissue gene expression

Hypothesis

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 achieving at least a 50% reduction of proteinuria with protocol specified steroid tapering regimen at Week 24.

OVERALL DESIGN

Main Study

This is a randomized, double-blind, placebo-controlled, parallel, multicenter, interventional Phase 2 study in participants aged 18 to 75 (inclusive) with active LN. The total duration of the original study was 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 4 additional weeks.

Unscheduled visits are permitted for reasons such as safety events or worsening of LN.

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. After all enrolled participants have completed the Week 20 visit, no additional study intervention will be administered. For further details, see End of Study Section of this synopsis.

A placebo comparator (in addition to standard-of-care background therapy) will be used in this study through Week 48 to allow for blinded, placebo-controlled evaluation of the long-term efficacy and safety of guselkumab in participants with LN. Participants will be stratified by geographic region and UPCR level.

Efficacy, safety, PK, immunogenicity, and biomarkers (where local regulations permit) will be assessed according to the Schedule of Activities. 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. Participants who experience an LN flare during the main study will be discontinued from study intervention.

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 (TB).

Long-Term Extension

Participants who achieve complete renal response (CRR) at Week 48 and complete the Week 52 assessments may have the option to participate in the long-term extension (LTE) of the study. The LTE begins after the assessments have been completed at Week 52. The objective of the LTE is to evaluate the efficacy and safety of long-term guselkumab treatment.

During the LTE, all participants will be assessed for safety and efficacy. Participants who experience an LN flare during the LTE will be discontinued from study intervention and will be required to complete the final efficacy/safety follow-up visits.

All study evaluations that should be performed during the LTE are listed in the SoA.

The study blind will be maintained throughout the study (including the LTE).

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.

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 Schedule of Activities (Section 1.3).

One database lock is planned at the end of study.

NUMBER OF PARTICIPANTS

An original target of approximately 60 participants were to be randomly assigned in this study 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.

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.

In addition to remaining on the SOC noted above, participants will be randomized to 1 of 2 treatment groups 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 remain on their assigned treatment through Week 48. All participants will receive an IV infusion at Weeks 0, 4, and 8 (either active or placebo) and 2 SC injections (either active or placebo) at Week 12 through Week 48.

If eligible for the LTE, participants will continue to receive the same study intervention that they were assigned to receive through Week 48. The first dose in the LTE will be at Week 52, and the LTE will continue for up to 2 years.

EFFICACY EVALUATIONS

Investigator assessments and patient-reported outcomes (PROs) of efficacy include the following:

- SLEDAI-2K
- Physician's Global Assessment of Disease Activity (PGA)
- Joint count assessments
- CLASI
- PROs measures to assess: Lupus symptoms (Lupus Symptoms questionnaire), fatigue (FACIT-Fatigue), health-related quality of life (LupusQoL), and changes in disease severity (Patient Global Impression of Change – PGIC).

Efficacy evaluations also include laboratory assessments related to kidney function that include the primary endpoint and other key efficacy endpoints.

PHARMACOKINETIC EVALUATIONS

Serum samples will be used to evaluate the PK of guselkumab, as well as the immunogenicity of guselkumab (antibodies to guselkumab).

In addition, 24-hour urine samples will be used to evaluate the potential renal excretion of guselkumab.

IMMUNOGENICITY EVALUATIONS

Antibodies to guselkumab will be evaluated in serum samples collected from all participants according to the Schedule of Assessments (SoA). Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study.

PHARMACODYNAMIC AND BIOMARKER EVALUATIONS

Pharmacodynamic markers will be evaluated using blood and urine samples collected at visits as indicated in the SoA.

Biomarker assessments will be made to examine the biologic response to treatment and to identify biomarkers that are relevant to guselkumab treatment and/or LN, where local regulations permit. Assessments will include the evaluation of relevant biomarkers in serum, whole blood, and urine collected as specified in the SoA, where local regulations permit.

PHARMACOGENOMIC (DNA) EVALUATIONS

A pharmacogenomic blood sample will be collected from participants who consent separately to this component of the study to allow for pharmacogenomic research, where local regulations permit. Participation in pharmacogenomic research is optional.

SAFETY EVALUATIONS

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 TB.

STATISTICAL METHODS

Due to the Sponsor's decision to terminate the study early, some analyses described below may not be performed. The primary efficacy analysis and most secondary efficacy analyses will be performed. All safety analyses will be performed. Details will be described in the revised SAP.

For informational purposes, the below section outlines the original statistical plan.

Sample Size Determination

An original target of approximately 60 participants were planned to be enrolled into the study. 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 study will be considered a success if the 1-sided p-value from the difference in proportion of participants with ≥50% decrease in proteinuria between the guselkumab and placebo intervention groups from a logistic mixed effect repeat measurement (MMRM) longitudinal model is less than a 1-sided alpha of 10%.

The table below shows the sensitivity of power to detect a difference in proportions of participants with ≥50% decrease in proteinuria between the guselkumab and placebo intervention groups at Week 24.

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.

Primary Endpoint Analysis

Analyses of the primary efficacy endpoint (≥50% decrease in proteinuria from baseline at Week 24) will include data from all randomized participants who received at least one administration of study intervention based on their assigned intervention group, regardless of the actual intervention received and have baseline data (Evaluable population).

Treatment Failure Criteria may include: initiation or increased use of a glucocorticoid or other immunosuppressive agents, however these will be further defined in the SAP.

Participants who meet any of the TF criteria defined in the SAP will be assumed a non-responder, ie, did not meet the ≥50% decrease in proteinuria criteria at Week 24.

The primary analysis will be based on the composite estimand where participants meeting TF criteria are assumed non-achievers from the point of TF forward, and missing data are assumed as non-achievers as well.

The study will be considered a success if the 1-sided p-value from the difference in proportion of participants with ≥50% decrease in proteinuria between the guselkumab and placebo intervention groups from a logistic MMRM longitudinal model is less than a 1-sided alpha of 10%.

See the SAP for further details about the analysis of the primary endpoint, including sensitivity and subgroup analyses.

Major Secondary Analyses

The major secondary endpoints are listed above. The Evaluable population will be used for analysis and participants will be counted in the intervention group assigned, regardless of the study intervention received.

Treatment failure and missing data will be included in the secondary endpoint estimands as non-achievers or non-responders.

The details of the analysis of the major secondary endpoints will be included in the SAP.

Safety Analyses

The following analyses of AEs will be used to assess the safety of participants:

- Frequency and type of AEs.
- Frequency and type of SAEs.
- Frequency and type of reasonably related AEs as assessed by the investigator.
- Frequency and type of AEs leading to discontinuation of study intervention.
- Frequency and type of infections, serious infections, and infections requiring oral or parenteral antimicrobial treatment.
- Frequency and type of AEs temporally associated with an infusion.
- Frequency and type of injection-site reactions.

Summaries, listings, datasets, or participant narratives may be provided through Week 24 and Week 60, by treatment intervention, for the above AEs, deaths, and severe AEs. Selected safety summaries will also be performed for participants of the LTE.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test over time, and by treatment intervention. CTCAE toxicity grades (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled timepoint.

Vital Signs

Blood pressure (systolic and diastolic) will be summarized over time, using descriptive statistics and/or graphically. The percentage of participants with values beyond clinically important limits will be summarized.

Other Analyses

Pharmacokinetic Analyses

Serum guselkumab concentrations will be summarized over time for all participants who receive at least 1 dose of guselkumab. Descriptive statistics will be calculated at each sampling timepoint.

Urine guselkumab concentrations will be summarized in a separate report.

Immunogenicity Analyses

The incidence of anti-guselkumab antibodies will be summarized for all participants who receive at least 1 dose of guselkumab and have appropriate samples for detection of antibodies to guselkumab (ie, participants with at least 1 sample obtained after their first dose of guselkumab).

The incidence of neutralizing antibodies (NAbs) to guselkumab will be summarized for participants who are positive for antibodies to guselkumab and have samples evaluable for NAbs to guselkumab.

Biomarkers Analyses

Changes in serum protein analytes may be summarized for the induction period and summarized by treatment group for the maintenance period. Associations between baseline levels and changes from baseline in select markers and response to treatment may be explored. Ribonucleic acid (RNA) analyses from cells in blood or urine may be summarized in a separate technical report.

Pharmacokinetic/Pharmacodynamic Analyses

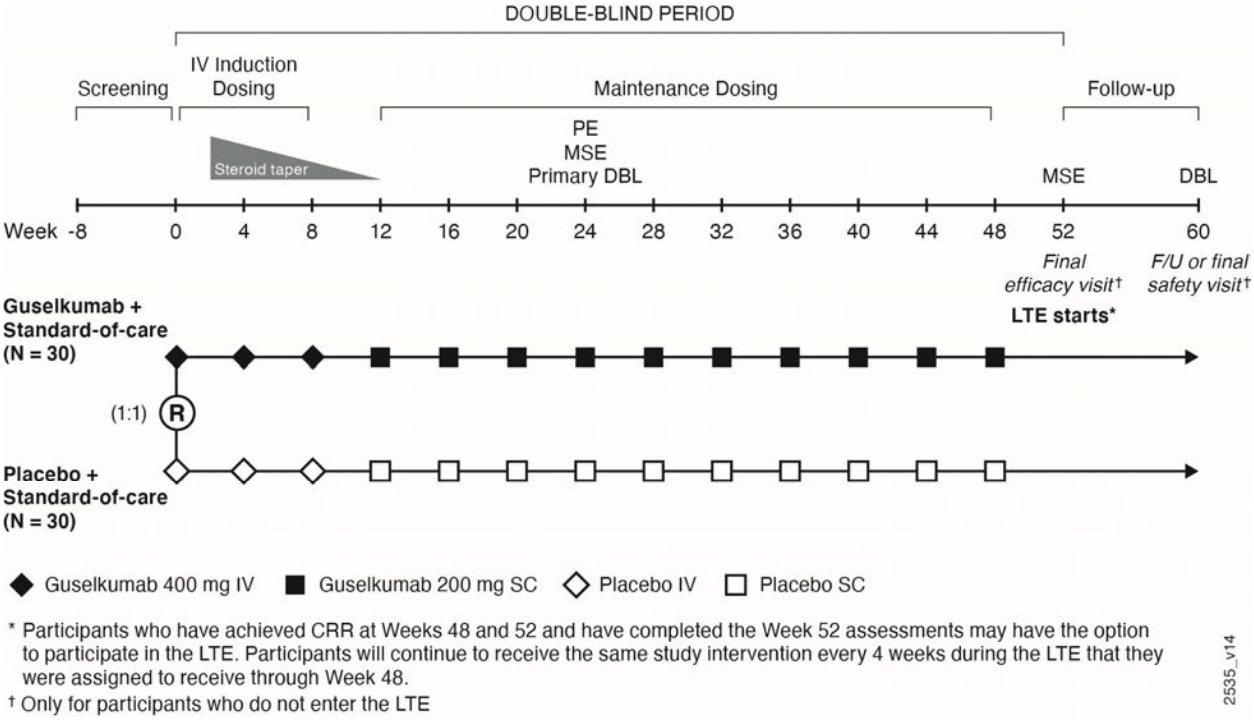
The relationship between serum concentrations of guselkumab and the efficacy measures and/or relevant PD endpoints may be explored graphically when appropriate. If any visual trend is observed, additional analysis may be conducted if deemed necessary, and will be described in a separate report if performed.

Pharmacogenomic Analyses

Genetic (deoxyribonucleic acid [DNA]) analyses will be conducted only in participants who sign the consent form to participate in the pharmacogenomic sampling. These analyses are considered exploratory and may be summarized in a separate technical report.

1.2. Schema

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.

1.3. Schedule of Activities (SoA)

Table 1: Schedule of Activities – Main Study (Screening Through Week 60)

Phase	Screening[a]	Double-blind Period															Follow-up	Notes
Week[b]	(≤8 Weeks)	0	D2	4	8	12	16	20	24	28	32	36	40	44	48	52/Final Efficacy Visit[c,f]	60 or Final Safety Visit[d,g]	
Study Procedure																		
Screening/Administrative																		
Informed consent	X																	Must be signed before first study related activity.
ICF for optional genetic research samples	X																	
Demographics	X																	
Review medical history requirements	X																	
Review prestudy therapy	X																	Detailed information of prestudy topical and systemic SLE and LN therapies including dosage and frequency of administration must be recorded for past history. Other prestudy therapies administered at the time of screening or up to 60 days before the first dose of study intervention, whichever is longer, must be recorded on the eCRF.
Inclusion/exclusion criteria	X	X																Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Source Documents section of Appendix 9, Regulatory, Ethical, and Study Oversight Considerations. Check clinical status again before first dose of study intervention.
12 lead ECG	X																	
QuantiFERON TB® test	X																	All participants will undergo QuantiFERON® TB testing. If the QuantiFERON® TB test is not approved/registered in the country in which this protocol is being conducted or the tuberculin skin test is mandated by local health authorities, a negative tuberculin skin test result is also required. In Ukraine, while the QuantiFERON® TB test is not approved/registered, it is accepted, and a tuberculin skin test is not required.

Table 1: Schedule of Activities – Main Study (Screening Through Week 60)

Phase	Screening[a]	Double-blind Period														Follow-up	Notes
Week[b]	(≤8 Weeks)	0	D2	4	8	12	16	20	24	28	32	36	40	44	48	52/Final Efficacy Visit[c,f]	60 or Final Safety Visit[d,g]	
Study Procedure																		
Tuberculin skin test	X																	Only required if QuantiFERON® TB is not registered/approved or accepted locally or the TST is mandated by local health authorities.
HBV and HCV testing	X																	See Appendix 4 for details.
HIV test	X																	
Chest x ray	X																	Chest x ray posterior/anterior and lateral views (or per country regulations where applicable) must be taken within 12 weeks prior to randomization and read by a qualified radiologist (or pulmonologist in accordance with local regulations), with no evidence of current, active TB or old, inactive TB. A chest computed tomography (CT) scan, obtained outside of the protocol, is also acceptable instead of a chest radiograph.
SLE classification by 2019 EULAR/ACR criteria	X																	The 2019 EULAR/ACR criteria are provided in Appendix 2 (Section 10.2).
Renal biopsy Class III/IV Activity	X																	For participants not having a previous renal biopsy (within the last 6 months prior to screening), one must be performed during screening. The pathology report documenting renal biopsy Class III/IV (based on ISN/RPS histology criteria) activity should be submitted to the sponsor. Tissue samples to assess for biomarker analysis should be sought for all renal biopsies for all participants who consent.
Study Intervention Administration																		
Randomization		X																
Study intervention infusion (at study site)		X		X	X													Participants should remain for observation for 1 hr following the infusion.
Study intervention SC injection (at study site)						X	X	X	X	X	X	X	X	X	X			Participants should remain for observation for 30 minutes following the injections.
Efficacy Assessments																		
PROs																		Whenever possible, patient reported outcome assessments should be conducted before any tests, procedures, or other consultations for

Table 1: Schedule of Activities – Main Study (Screening Through Week 60)

Phase	Screening[a]	Double-blind Period															Follow-up	Notes
Week[b]	(≤8 Weeks)	0	D2	4	8	12	16	20	24	28	32	36	40	44	48	52/Final Efficacy Visit[c,f]	60 or Final Safety Visit[d,g]	
Study Procedure																		
																		that visit to prevent influencing participants' perceptions. It is recommended that PROs be performed in the following sequence: FACIT fatigue, PGIC, lupus symptoms (assessment of joint pain, joint stiffness, rash, and swelling), and LupusQoL.
FACIT Fatigue		X				X			X							X		
PGIC									X							X		
Lupus Symptoms		X				X			X			X				X		
LupusQol		X							X							X		
ClinROs																		ClinRO portion to be completed by the investigator/designee at all sites.
SLEDAI 2K	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
PGA of Disease Activity	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Joint count assessment	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Cutaneous lupus (CLASI)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Repeat renal biopsy (optional)																X[h]		The pathology report should be submitted to the sponsor. Tissue samples to assess for biomarker analysis should be sought for all renal biopsies for all participants who consent.
Safety Assessments																		
Full physical examination	X																X	A physical examination will be performed at screening and the Week 60/Final safety follow up visit. The head and neck, chest, abdomen, and extremities should be examined, as well as including examinations based on the individual's medical history and manifestations of SLE and LN (edema, skin manifestations, arthritis, etc.).
Targeted physical examination		X		X	X	X	X	X	X	X	X	X	X	X	X	X		Targeted physical examination should also include evaluation of signs or symptoms of infection.
Vital signs	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height	X																	
Weight	X	X							X							X		

Table 1: Schedule of Activities – Main Study (Screening Through Week 60)

Phase	Screening[a]	Double-blind Period														Follow-up	Notes
Week[b]	(≤8 Weeks)	0	D2	4	8	12	16	20	24	28	32	36	40	44	48	52/Final Efficacy Visit[c,f]	60 or Final Safety Visit[d,g]	
Study Procedure																		
TB evaluation	X	X			X		X		X		X		X		X	X	X	TB evaluation includes an assessment of recent exposure or risk of TB including new or chronic cough, fever, night sweats, unintentional weight loss or recent contact with someone with active TB. If TB is suspected at any time during the study, a chest x ray (consistent with local regulations), and QuantiFERON® TB test should be performed. A TST is additionally required if the QuantiFERON® TB test is not registered/approved locally or the TST is mandated by local health authorities.
Urine pregnancy test	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	Females of childbearing potential only. A serum pregnancy test may be conducted at screening at the discretion of investigator or if required by local regulations.
Review concomitant therapy	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Glucocorticoid tapering		<Weeks 2 to 12>																See Section 6.5.2 and Appendix 7 (Section 10.7) for information on glucocorticoid tapering.
Adverse events	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	AE review should include review and documentation of medical history including information about seeking medical attention or hospitalizations that occur between study visits.
eC SSRS	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	At the screening visit, the eC SSRS should be completed as the first assessment after signing informed consent and before any other tests, procedures, or other consultations. For subsequent visits, the eC SSRS should be completed after all PROs and before any other tests, procedures, or other consultations.
Infusion or injection site reaction evaluation		X		X	X	X	X	X	X	X	X	X	X	X	X			Participants should be monitored for the occurrence of infusion or injection site reactions for 60 or 30 minutes after the study intervention administration, IV infusion or SC injection, respectively.

Table 1: Schedule of Activities – Main Study (Screening Through Week 60)

Phase	Screening[a]	Double-blind Period															Follow-up	Notes
Week[b]	(≤8 Weeks)	0	D2	4	8	12	16	20	24	28	32	36	40	44	48	52/Final Efficacy Visit[c,f]	60 or Final Safety Visit[d,g]	
Study Procedure																		
Clinical Laboratory Tests																		
Chemistry	X[e]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Cystatin C	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Lipid panel (fasting)		X							X							X		For fasting laboratory assessments, if the participant has not fasted before the visit, the visit may proceed, a note should be made in the laboratory requisition form that the participant had not fasted.
Hematology	X[e]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Anti CCP/RF	X																	
Flow cytometry	X																	Perform test clinical B cell flow cytometry analyses at screening for participants previously exposed to B cell depleting therapies (eg, rituximab and obinutuzumab).
Coagulation	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	This refers to PT, PTT, and INR.
Antinuclear antibodies	X															X		
Anti dsDNA, C3, C4	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Other autoantibodies	X	X							X							X		Other autoantibodies include testing for anti Smith, SSA anti Ro, SSB anti La, anti RNP.
Anti phospholipid antibodies	X	X							X							X		This testing includes: anti cardiolipin IgG and IgM, anti Beta2 glycoprotein IgG and IgM, and lupus anticoagulant. If an abnormal test result is not obtained at Screening or Week 0, no additional follow up testing is required. However, additional testing may be performed if clinically indicated.
Ig isotype profile		X							X							X		
Urine Analyses (spot urine)																		
Urinalysis (dipstick, all participants)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X[h]	X	
Urine sample for biomarkers (where local regulations permit)	X	X		X	X	X	X	X	X				X			X[h]		This urine sample will need to be processed as per the procedure in the laboratory manual including centrifugation, with the supernatant frozen and the pellet cryopreserved.
Urine protein/creatinine ratio	2X[e]	X		X	X	X	X	X	X	X	X	X	X	X	X	X[h]	X	The UPCR must be collected on first morning void specimens. Two urine specimen containers should be provided prior to visits for this collection.

Table 1: Schedule of Activities – Main Study (Screening Through Week 60)

Phase	Screening[a]	Double-blind Period														Follow-up	Notes
Week[b]	(≤8 Weeks)	0	D2	4	8	12	16	20	24	28	32	36	40	44	48	52/Final Efficacy Visit[c,f]	60 or Final Safety Visit[d,g]	
Study Procedure																		
Urine sediment analysis	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X[h]		
24-hour urine analyses																		
Urine protein/creatinine ratio	Give urine jug for Wk0 collection	X						jug	X						jug	X[h]		Give urine jug during screening for Week 0 collection. Give urine jug at the Week 20 and Week 48 visits for Week 24 and Week 52 collections.
24 hr urine for PK		X	X															1. At Week 0 predose, the 24 hour PK urine samples will be taken from the 24 hour urine collection for urine protein and creatinine. 2. A post dose sample will be taken starting with the first void after the start of the first infusion and ending with the last void within 24 hours of the end of the first infusion. The sample will be returned to the study site at the Day 2 visit (+24 hour window).
Pharmacokinetics/Immunogenicity																		
Serum guselkumab concentrations		2X	X	X	X	X	X	X	X			X				X	X	1. At Week 0, 2 separate samples for serum guselkumab concentrations (indicated by "2X" in the SoA) will be collected (1 sample will be collected prior to the IV infusion and the other collected 1 hour after the end of the infusion) for all participants. For all other visits that include study intervention administration, only a predose serum guselkumab concentration sample will be collected. 2. For visits with study intervention administration, all blood samples for assessing predose guselkumab concentration and antibodies to guselkumab MUST be collected BEFORE the administration of the study intervention. 3. When both PK/ADA samples are collected, one sample (instead of 2) will be collected for both assays.

Table 1: Schedule of Activities – Main Study (Screening Through Week 60)

Phase	Screening[a]	Double-blind Period														Follow-up	Notes
Week[b]	(≤8 Weeks)	0	D2	4	8	12	16	20	24	28	32	36	40	44	48	52/Final Efficacy Visit[c,f]	60 or Final Safety Visit[d,g]	
Study Procedure																		
Population PK		← X → (Weeks 0 to 4)				← X → (Weeks 12 to 16)												These are additional study visits, at which a venous blood sample for population PK analysis will be collected from all participants. This random sample collection must occur on any day in each of the 2 designated time periods except on the days of scheduled study visits. Additionally, this blood sample must be collected at least 24 hours prior to or after the actual time of study intervention administration. Note: This random sample may not be drawn on the Day 2 visit.
Antibodies to study intervention		X		X	X	X			X			X				X	X	When both PK/ADA samples are collected, one sample (instead of 2) will be collected for both assays.
Pharmacogenomics (DNA)																		
Blood sample collection (optional)	X								X							X		The pharmacogenomic (DNA) sample should be collected at the specified timepoint, however if necessary, it may be collected at a later timepoint. The screening sample should be collected no later than prior to randomization.
Blood Biomarkers (where local regulations permit)																		
Serum biomarkers	X	X		X	X	X	X	X	X		X		X		X	X		
Whole blood (RNA)	X	X		X	X	X			X				X			X		
PBMC (cellular analysis)	X	X				X			X				X			X		Whole blood will be collected and processed for PBMC cryopreservation.

Abbreviations: ACR American College of Rheumatology; ADA anti drug antibodies; AE adverse events; anti CCP anti cyclic citrullinated peptide; anti RNP anti ribonucleoprotein; CLASI Cutaneous Lupus Erythematosus Disease Area and Severity Index; ClinROs Clinical Reported Outcomes; DNA deoxyribonucleic acid; dsDNA double stranded DNA; ECG electrocardiogram; eCRF electronic case report form; eC SSRS electronic Columbia Suicide Severity Rating Scale; EULAR European League Against Rheumatism; FACIT Functional Assessment of Chronic Illness Therapy; HBV hepatitis B virus; HCV hepatitis C virus; HIV human immunodeficiency virus; ICF informed consent form; Ig immunoglobulin; INR International Normalized Ratio; ISN/RPS International Society of Nephrology/Renal Pathology Society; IV intravenous; LN lupus nephritis; PBMC peripheral blood mononuclear cell; PGA Physician's Global Assessment; PGIC Patient Global Impression of Change; PK pharmacokinetics; PRO patient reported outcomes; PT prothrombin time; PTT partial thromboplastin time; RF rheumatoid factor; RNA ribonucleic acid; SC subcutaneous; SLE systemic lupus erythematosus; SLEDAI 2K SLE disease activity index 2000; SSA anti Ro anti Sjögren's syndrome related antigen A; SSB anti La anti Sjögren's syndrome related antigen B; TB tuberculosis; TST tuberculin skin test; UPCR Urine Protein to Creatinine Ratio; Wk Week.

Footnotes:

a. Screening visit must be performed no more than 8 weeks prior to the randomization visit (Week 0). Screening may be extended by up to 4 additional weeks for participants who start MMF/MPA at or near (within 2 weeks before) the beginning of screening to allow for repeat of laboratory entry criteria after 8 weeks of mycophenolate mofetil (MMF)/ mycophenolic acid (MPA) treatment.

b. Administration of study intervention and visit window must be within ±7 days of the scheduled visit date. Unless otherwise specified, all assessments (except for infusion/injection-site evaluation) are to be completed prior to study intervention administration.

c. For participants who discontinue study intervention administrations, every effort should be made to conduct final efficacy and safety assessments. Participants who permanently discontinue study intervention, but do not withdraw from study participation, should be followed at all subsequent study visits through Week 60. Week 52 may serve as the final safety follow-up visit if study medication was stopped on or before Week 40, but a full physical exam should be performed at that visit (Week 52). Sites will be notified after all enrolled participants have completed the Week 20 visit or discontinued study intervention prior to Week 24. Participants who are receiving study intervention will then complete a final efficacy visit approximately 4 weeks after the last administration of study intervention and the final safety follow-up visit approximately 12 weeks after the last administration of study intervention.
d. Participants who discontinue study intervention administrations and do not wish to continue in the study should return 12 weeks after the last study intervention administration for a final safety follow-up visit and complete assessment as indicated for Week 60.
e. Chemistry, hematology, and UPCR (x2) must be completed after the participant has received at least 8 weeks of MMF/MPA.
f. Refer to Table 2 for additional Week 52 assessments to be performed for participants who continue in the long-term extension (LTE).
g. These assessments will be performed for participants who complete their Week 52 visit, but do not enter the LTE.
h. Urinalysis assessments should not be done within 48 hours after biopsy to limit possible blood from biopsy in urine.

Table 2: Schedule of Activities – Long-term Extension for Eligible Participants (through Week 104)

Week	52[a]	56	60	64	68	72	76	80	84	88	92	96	100	104	Final Efficacy Visit[b]	Final Safety Follow-up Visit[c]	Notes
Study Procedure[d]																	
Visit Window	± 7 days																
Administrative																	
Informed consent	X																Confirm participant consented to participate in LTE
Provide/Collect and review participant diary card			X		X		X		X		X		X				For participant/caregiver who is administering study intervention at home. Training should be provided at Week 60 or initial dispensation.
Study Intervention Administration																	
Instruction for self administration			X														At home administration by participant/caregiver is at the investigator's and participant's discretion, and upon completion of training. Participant/caregiver will administer the first dose in the LTE at Week 60 in the presence of qualified study site staff and subsequent administrations of study intervention can be self administered by the participant/caregiver at home.
Dispense study intervention to participant/caregiver			X		X		X		X		X		X				Dispense study intervention to participant/caregiver who will administer next dose of study intervention at home.
Study intervention SC injection (at site/at home)	X	X	X	X[e]	X	X[e]	X	X[e]	X	X[e]	X	X[e]	X	X[e]			At home administration may begin with Week 64 administration of study intervention according to regional/local regulations and instructions. Participants will have option of continuing to receive injections at site by study site personnel. The PFS Y drug device (a prefilled syringe with autoinjector) will be used for at home administration. The PFS Y or PFS U could be used at site for study intervention administration by site staff depending on availability. If PFS Y is not available at site for at home administration, then administration of study intervention will occur at study site.

Table 2: Schedule of Activities – Long-term Extension for Eligible Participants (through Week 104)

Week	52[a]	56	60	64	68	72	76	80	84	88	92	96	100	104	Final Efficacy Visit[b]	Final Safety Follow-up Visit[c]	Notes
Efficacy Assessments																	
PROs																	Whenever possible, PRO assessments should be conducted before any tests, procedures, or other consultations for that visit to prevent influencing participants' perceptions. It is recommended that PROs be performed in the following sequence: FACIT Fatigue, PGIC, lupus symptoms (assessment of joint pain, joint stiffness, rash, and swelling), and LupusQoL
FACIT Fatigue					X				X				X		X		
PGIC					X				X				X		X		
Lupus Symptoms					X				X				X		X		
LupusQoL					X				X				X		X		
ClinROs																	ClinRO portion to be completed by the investigator/designee at all sites.
SLEDAI 2K					X				X				X		X		
PGA of Disease Activity					X				X				X		X		
Joint Count Assessment					X				X				X		X		
Cutaneous Lupus (CLASI)					X				X				X		X		
Safety Assessments																	
Full physical examination																X	
eC SSRS			X		X		X		X		X		X		X	X	
Targeted physical examination		X	X		X		X		X		X		X		X		
Vital signs		X	X		X		X		X		X		X		X	X	
Weight							X						X		X		
TB evaluation		X	X		X		X		X		X		X		X	X	TB evaluation includes an assessment of recent exposure or risk of TB including new or chronic cough, fever, night sweats, unintentional weight loss or recent contact with someone with active TB. If TB is suspected at any time during the study, a chest x ray (consistent with local regulations), and QuantiFERON® TB test should be performed. A TST is additionally required if the QuantiFERON® TB test is not registered/approved locally or the

Table 2: Schedule of Activities – Long-term Extension for Eligible Participants (through Week 104)

Week	52[a]	56	60	64	68	72	76	80	84	88	92	96	100	104	Final Efficacy Visit[b]	Final Safety Follow-up Visit[c]	Notes
																	TST is mandated by local health authorities.
Urine pregnancy test (β HCG)		X	X		X		X		X		X		X		X	X	Females of childbearing potential only
Review concomitant therapy		X	X		X		X		X		X		X		X	X	
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Participants/caregiver who administer study intervention at home will be asked to identify signs or symptoms related to AEs before study intervention administration and will be asked to contact the study doctor before administration if a symptom is identified.
Injection site evaluation		X	X	X	X	X	X	X	X	X	X	X	X	X			Participants who receive study intervention at site should be monitored for injection site reaction post injection; duration of observation period is at investigator's discretion. Participants/caregivers who will administer study intervention at home will be trained to perform self evaluation for injection site reactions and report adverse events.
Clinical Laboratory Tests																	
Chemistry			X		X		X		X		X		X		X	X	
Cystatin C			X		X		X		X		X		X		X	X	
Hematology			X		X		X		X		X		X		X	X	
Coagulation					X				X				X		X		
Antinuclear antibodies															X		
Anti dsDNA, C3, C4					X				X				X		X	X	
Other autoantibodies					X				X				X		X	X	
Anti phospholipid antibodies					X				X				X		X	X	If an abnormal test result is not obtained at Screening or Week 0, no additional follow up testing is required. However, additional testing may be performed if clinically indicated.
Ig isotype profile					X				X				X		X	X	
Urine Analyses (spot urine)																	
Urinalysis (dipstick, all participants)			X		X		X		X		X		X		X	X	
Urine protein/creatinine ratio			X		X		X		X		X		X		X	X	Must be collected on first morning void specimens.

Table 2: Schedule of Activities – Long-term Extension for Eligible Participants (through Week 104)

Week	52[a]	56	60	64	68	72	76	80	84	88	92	96	100	104	Final Efficacy Visit[b]	Final Safety Follow-up Visit[c]	Notes
Urine sediment analysis			X		X		X		X		X		X		X		
Pharmacokinetic/Immunogenicity Assessments																	
Serum guselkumab concentrations[f]							X						X		X	X	
Antibodies to study intervention[f]							X						X		X	X	
Biomarkers (where local regulations permit)																	
Serum biomarkers													X		X		
Urine biomarkers													X		X		This sample needs to be processed as per the procedure in the laboratory manual, with centrifugation and freezing of the supernatant.
Whole blood (RNA)													X		X		
Pharmacogenomics (DNA)																	
Blood sample collection (optional)															X		

Abbreviations: ADA anti drug antibody; AE adverse events; β HCG beta human chorionic gonadotropin; CLASI Cutaneous Lupus Erythematosus Disease Area and Severity Index; ClinROs Clinical Reported Outcomes; DNA deoxyribonucleic acid; dsDNA double stranded DNA; eC SSRS electronic Columbia Suicide Severity Rating Scale; FACIT Functional Assessment of Chronic Illness Therapy; Ig immunoglobulin; LTE long term extension; LupusQoL Lupus Quality of Life; PFS U prefilled syringe with an UltraSafe Plus™ Passive Needle Guard; PFS Y prefilled syringe with YpsoMate autoinjector; PGA Physician's Global Assessment; PGIC Patient Global Impression of Change; PK pharmacokinetics; PRO patient reported outcomes; RNA ribonucleic acid; SC subcutaneous; SLEDAI 2K SLE disease activity index 2000; TB tuberculosis; TST tuberculin skin test.

Footnotes:

a. Refer to Table 1 for additional Week 52 assessments that must be performed.
b. These assessments should be performed at the time of study intervention discontinuation, at the time of study participation termination, or upon notification to sites of early study termination.
c. These assessments should be performed approximately 12 weeks after a participant's last dose of study intervention (for participants who have not withdrawn consent).
d. Unless otherwise specified, all assessments (except for injection site evaluation) are to be completed prior to study intervention administration.
e. Study intervention may be administered at home by trained participant/caregiver.
f. For visits with study intervention administration, all blood samples for assessing predose guselkumab concentration and antibodies to study intervention MUST be collected BEFORE the administration of the study intervention. When both PK/ADA samples are collected, 1 sample (instead of 2) will be collected for both assays.

Table 3: Schedule of Activities – Long-term Extension for Eligible Participants (Weeks 108 to 160)

Week	108	112	116	120	124	128	132	136	140	144	148	152/ Final Efficacy Visit[a]	160/Final Safety Follow-up Visit[b]	Notes
Study Procedure[c]														
Visit Window	**± 7 days**													
Administrative														
Provide/Collect and review participant diary card	X		X		X		X		X		X			For participant/caregiver who is administering study intervention at home. Training should be provided at Week 60 or initial dispensation.
Study Intervention Administration														
Dispense study intervention to participant/caregiver	X		X		X		X		X					Dispense study intervention to participant/caregiver who will administer next dose of study intervention at home.
Study intervention SC injection (at site/at home)	X	X[d]	X	X[d]	X	X[d]	X	X[d]	X	X[d]	X			At home administration may begin with Week 64 administration of study intervention according to regional/local regulations and instructions. Participants will have option of continuing to receive injections at site by study site personnel. The PFS Y drug device (a prefilled syringe with autoinjector) will be used for at home administration. The PFS Y or PFS U could be used at site for study intervention administration by site staff depending on availability. If PFS Y is not available at site for at home administration, then administration of study intervention will occur at study site.
Efficacy Assessments														
PROs														Whenever possible, patient reported outcome assessments should be conducted before any tests, procedures, or other consultations for that visit to prevent influencing participants' perceptions. It is recommended that PROs be performed in the following sequence: FACIT fatigue, PGIC, lupus symptoms (assessment of joint pain, joint stiffness, rash, and swelling), and LupusQoL
FACIT Fatigue			X				X					X		
PGIC			X				X					X		
Lupus Symptoms			X				X					X		
LupusQoL			X				X					X		
ClinROs														ClinRO portion to be completed by the investigator/designee at all sites.
SLEDAI 2K			X				X					X		
PGA of Disease Activity			X				X					X		
Joint Count Assessment			X				X					X		
Cutaneous Lupus (CLASI)			X				X					X		
Safety Assessments														
Full physical examination													X	

Table 3: Schedule of Activities – Long-term Extension for Eligible Participants (Weeks 108 to 160)

Week	108	112	116	120	124	128	132	136	140	144	148	152/ Final Efficacy Visit[a]	160/Final Safety Follow-up Visit[b]	Notes
eC SSRS	X		X		X		X		X		X	X	X	
Targeted physical examination	X		X		X		X		X		X	X		
Vital signs	X		X		X		X		X		X	X	X	
Weight					X						X	X		
TB evaluation	X		X		X		X		X		X	X	X	TB evaluation includes an assessment of recent exposure or risk of TB including new or chronic cough, fever, night sweats, unintentional weight loss or recent contact with someone with active TB. If TB is suspected at any time during the study, a chest x ray (consistent with local regulations), and QuantiFERON® TB test should be performed. A TST is additionally required if the QuantiFERON® TB test is not registered/approved locally or the TST is mandated by local health authorities.
Urine pregnancy test (β HCG)	X		X		X		X		X		X	X	X	Females of childbearing potential only.
Review concomitant therapy	X		X		X		X		X		X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	Participants/caregiver who administer study intervention at home will be asked to identify signs or symptoms related to AEs before study intervention administration and will be asked to contact the study doctor before administration if a symptom is identified.
Injection site evaluation	X	X	X	X	X	X	X	X	X	X	X			Participants who receive study intervention at site should be monitored for injection site reaction post injection; duration of observation period is at investigator's discretion. Participants/caregivers who will administer study intervention at home will be trained to perform self evaluation for injection site reactions and report adverse events.
Clinical Laboratory Tests														
Chemistry	X		X		X		X		X			X	X	
Cystatin C	X		X		X		X		X			X	X	
Hematology	X		X		X		X		X			X	X	
Coagulation			X				X					X		
Antinuclear antibodies												X		
Anti dsDNA, C3, C4			X				X					X	X	
Other autoantibodies			X				X					X	X	
Anti phospholipid antibodies			X				X					X	X	If an abnormal test result is not obtained at Screening or Week 0, no additional follow up testing is required. However, additional testing may be performed if clinically indicated.
Ig isotype profile			X				X					X	X	
Urine Analyses (spot urine)														

Table 3: Schedule of Activities – Long-term Extension for Eligible Participants (Weeks 108 to 160)

Week	108	112	116	120	124	128	132	136	140	144	148	152/ Final Efficacy Visit[a]	160/Final Safety Follow-up Visit[b]	Notes
Urinalysis (dipstick, all participants)	X		X		X		X		X		X	X	X	
Urine protein/creatinine ratio	X		X		X		X		X		X	X	X	Must be collected on first morning void specimens.
Urine sediment analysis	X		X		X		X		X		X	X		
Pharmacokinetic/Immunogenicity Assessments														
Serum guselkumab concentrations[e]												X	X	
Antibodies to study intervention[e]												X	X	
Biomarkers (where local regulations permit)														
Serum biomarkers											X	X		
Urine biomarkers											X	X		This sample needs to be processed as per the procedure in the laboratory manual, with centrifugation and freezing of the supernatant.
Whole blood (RNA)											X	X		
Pharmacogenomics (DNA)														
Blood sample collection (optional)												X		

Abbreviations: ADA anti drug antibody; AE adverse events; β HCG beta human chorionic gonadotropin; CLASI Cutaneous Lupus Erythematosus Disease Area and Severity Index; ClinROs Clinical Reported Outcomes; DNA deoxyribonucleic acid; dsDNA double stranded DNA; eC SSRS electronic Columbia Suicide Severity Rating Scale; FACIT Functional Assessment of Chronic Illness Therapy; Ig immunoglobulin; LTE long term extension; LupusQoL Lupus Quality of Life; PFS U prefilled syringe with an UltraSafe Plus™ Passive Needle Guard; PFS Y prefilled syringe with YpsoMate autoinjector; PGA Physician's Global Assessment; PGIC Patient Global Impression of Change; PK pharmacokinetics; PRO patient reported outcomes; RNA ribonucleic acid; SC subcutaneous; SLEDAI 2K SLE disease activity index 2000; TB tuberculosis; TST tuberculin skin test.

Footnotes:

a. These assessments should be performed at Week 152, at the time of study intervention discontinuation, at the time of study participation termination, or upon notification to sites of early study termination.
b. These assessments should be performed at Week 160 or approximately 12 weeks after a participant's last dose of study intervention for participants who have not withdrawn consent.
c. Unless otherwise specified, all assessments (except for injection site evaluation) are to be completed prior to study intervention administration.
d. Study intervention may be administered at home by trained participant/caregiver.
e. For visits with study intervention administration, all blood samples for assessing predose guselkumab concentration and antibodies to study intervention MUST be collected BEFORE the administration of the study intervention. When both PK/ADA samples are collected, 1 sample (instead of 2) will be collected for both assays.

2. INTRODUCTION

Guselkumab (CNTO 1959) is a fully human immunoglobulin G1 lambda monoclonal antibody (mAb) that binds to human interleukin (IL)-23 with high affinity. The binding of guselkumab to IL-23 blocks the binding of extracellular IL-23 to the cell surface IL-23 receptor, inhibiting IL-23-specific intracellular signaling and subsequent activation and cytokine production. In this manner, guselkumab inhibits the biological activity of IL-23 in all in vitro assays examined.

Guselkumab has been approved for the treatment of adults with moderate to severe plaque psoriasis in the United States (US), European Union (EU), Canada, Japan, and a number of other countries worldwide. In addition, guselkumab has been approved for the treatment of psoriatic arthritis (PsA), generalized pustular psoriasis, erythrodermic psoriasis, and palmoplantar pustulosis in Japan.

Guselkumab is currently being developed in other diseases including for the treatment of patients with PsA, hidradenitis suppurativa (HS), familial adenomatous polyposis, Crohn's disease, and ulcerative colitis (UC). Phase 3 studies in PsA, a Phase 2/3 program in Crohn's disease, a Phase 2b/3 study in UC, and a Phase 2 study in HS are currently ongoing or planned globally.

For the most comprehensive nonclinical and clinical information regarding guselkumab, refer to the latest version of the Investigator's Brochure (IB) for guselkumab.

The term "study intervention" throughout the protocol, refers to study drug, as defined in Section 6.1, Study Interventions Administered.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

The term "participant" throughout the protocol refers to the common term "subject".

2.1. Study Rationale

Lupus is a heterogeneous autoimmune disease that includes a broad spectrum of clinical forms, ranging from those with lesions confined to the skin (cutaneous lupus erythematosus [CLE]) to others that involve 1 or more vital internal organs (systemic lupus erythematosus [SLE]). Renal involvement due to SLE is termed lupus nephritis (LN).

Clinicopathologic Class III (focal proliferative) and Class IV (diffuse proliferative) LN per the current classification system of International Society of Nephrology/Renal Pathology Society (ISN/RPS) are considered more severe and have a poorer prognosis than Class I (minimal disease) or Class II (mesangial proliferative). Both Class III and IV LN may have active (proliferative), inactive (sclerosing), or combined active and inactive lesions.[38] Approved therapies for active LN are lacking, and patients with Class III or IV disease have a 50 to 75% risk of end-stage renal disease requiring dialysis within 10 years.[37] There is a high unmet need for new treatment options in LN that are safe and effective, especially new therapies that can provide improved long-term efficacy (ie, sustained remission) over currently available therapies (Section 2.1.1).

The Phase 2 clinical development program for guselkumab for active Class III or IV LN will evaluate the safety and efficacy of guselkumab added to standard-of-care compared to placebo added to standard-of-care. This study was originally planned to enroll a target of approximately 60 participants with a total duration of up to approximately 68 weeks. 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.

An overview of the protocol design and supportive rationale is described in Section 4.

The clinical and scientific rationale in support of the overall development program is described in Section 2.1.2.

Relevant background information on the nonclinical and clinical development of guselkumab is summarized in Section 2.2.

2.1.1. Unmet Need in Lupus Nephritis

There are limited treatments approved to treat LN globally, although cyclophosphamide and some glucocorticoids are approved to treat LN in the EU. However, the combination of a high-dose glucocorticoid in combination with cyclophosphamide or mycophenolate mofetil (MMF)/mycophenolic acid (MPA) is an off-label treatment that has become standard-of-care in more active forms of LN. Belimumab and voclosporin have been approved in the United States for adults with active LN who are receiving standard background immunosuppressive therapy regimens.[3,20] Despite these treatments, there is still a high rate of treatment failures (TFs) and progression to end-stage renal disease, highlighting the significant unmet medical need for more effective therapies, especially over the longer term. [11,26,32]

2.1.2. Rationale for Targeting IL-23 in Lupus Nephritis

Lupus nephritis is a manifestation of SLE affecting up to 60% of SLE patients at some point in their disease course. The hallmark in the pathogenesis of LN is autoantibody production and an immune complex formation with infiltration of inflammatory cells in renal tissue.[42] Anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies and also antinucleosome antibodies are specific to SLE and are more highly associated with incidence or flare of LN than with other organ manifestations, both in human disease and in murine models.[2,22,23,25,34,39] Remission of LN is associated with decreases in anti-deoxyribonucleic acid (DNA) antibody levels.[13,19]

Interleukin-23 is important for the generation and maintenance of T-helper (Th)17 cells. There is evidence which suggests that Th17 cells are involved in SLE and LN, including the detection of IL-17+ T cells in the kidneys of SLE patients with nephritis.[15,42] Additionally, IL-17+ T cells have been reported in the spleen and kidney of lupus-prone mice, and these cells have a higher expression of IL-23 receptors in the mice as they age and disease progresses.[15] Studies have shown that IL-23 is released from antigen presenting cells, which induces expansion of Th17 cells, forming what is known as the IL-23/IL-17 axis.[18,42] Additionally, other studies have shown high serum levels of IL-23 in LN.[4,40,42]

In a proof-of-concept preclinical mouse study, a mAb targeting IL-23 was given to lupus-prone mice with nephritis. Control mice developed pyuria and proteinuria. Anti-IL-23 treated mice did not develop pyuria, developed lower levels of proteinuria than the control treated mice, and exhibited a decrease in IL-17 production.[15] An IL-23 receptor deficiency has also been shown to prevent development of nephritis in mice.[16,42]

A study completed in Polish patients with SLE showed correlation between elevated IL-23 and patients having LN[8]; similar data was also shown in study in Chinese patients.[41] In a 2015 clinical study, 50 patients with active LN had biopsies taken at baseline and after treatment (eg, cyclophosphamide, or MMF + glucocorticoids). Those not responding to treatment (persistent proteinuria >0.5 gram/day) were found to have higher levels of IL-23 than others after treatment, while higher IL-17 at baseline was found in those with poor histological response (eg, persisting active nephritis).

Taken together, these data support the scientific rationale for further evaluation of an IL-23 inhibitor in patients with LN. In this study, guselkumab, a human mAb directed against the p19 subunit of the IL-23, and thus inhibits IL-23, will be evaluated.

2.2. Background

2.2.1. Nonclinical Studies

A full nonclinical development program was conducted with guselkumab to support the development of guselkumab for psoriasis and other indications in accordance with International Conference on Harmonisation (ICH) and other applicable guidelines. A comprehensive overview of nonclinical data is presented in Section 3 of the guselkumab IB. Details on the nonclinical studies supporting dosing is detailed in Section 4.3.

Nonclinical Pharmacology

Guselkumab has been shown to be pharmacologically active. Guselkumab prevents binding of IL-23 to the IL-23 receptor and subsequent activation of intracellular signaling pathways. In vitro studies have demonstrated that guselkumab inhibits the biological activity of human and non-human primate IL-23.

Nonclinical Safety Pharmacology

In nonclinical toxicology assessments, no adverse effects of guselkumab were observed in safety pharmacology evaluations following single or repeated dosing of cynomolgus monkeys via intravenous (IV) and subcutaneous (SC) routes of administration at doses up to 50 mg/kg once weekly for up to 6 months. Additionally, guselkumab was well-tolerated during a cardiovascular (CV) safety pharmacology assessment in monkeys.

Nonclinical Pharmacokinetics

The pharmacokinetics (PK) of guselkumab was investigated in male cynomolgus monkeys following a single IV or SC administration of guselkumab. Monkeys were treated with a single IV dose of guselkumab at 50 mg/kg or a single SC dose of guselkumab at 1, 10, or 50 mg/kg. The maximum observed concentration (C_{max}) and area under the serum concentration versus time curve

from time 0 to infinity with extrapolation of the terminal phase (AUC_{inf}), appeared to increase dose proportionally from 10 to 50 mg/kg, but less than dose proportionally from 1 to 10 mg/kg. The observed time to maximal concentration (T_{max}) was 1 to 5 days after SC administration. The mean elimination half-life ($T_{1/2}$) after SC administration ranged from 7 to 10 days.

The PK of guselkumab was assessed as part of a 5-week (Phase 1) and 6-month (Phase 2) toxicology study in cynomolgus monkeys. In Phase 1, the systemic exposure of guselkumab increased in an approximately dose proportional manner over the dose range of 10 to 50 mg/kg after SC administration. In Phase 2 of the study, the C_{max} and area under the curve (AUC) within 1 dose interval increased in an approximately dose proportional manner at steady-state following weekly SC administration of guselkumab.

Nonclinical Toxicology

Administration of guselkumab was not associated with any toxicologically significant findings in repeat dose toxicity studies in cynomolgus monkeys (once weekly) or guinea pigs (twice weekly); these are the pharmacologically relevant species for the evaluation of the general and developmental toxicity assessment of guselkumab. No evidence of CV effects was noted in cynomolgus monkeys in a CV safety pharmacology assessment at IV doses of 10 and 50 mg/kg, or during the 5-week (IV/SC)/24-week (SC) study at doses up to 50 mg/kg that included assessments for CV liability. Guselkumab had no effects in pregnant cynomolgus monkeys or their infants following once per week SC doses up to 50 mg/kg in an enhanced prenatal and postnatal development study. Fertility and early embryo/fetal development were unaffected in the male and female guinea pig following twice weekly SC administration of 25 and 100 mg/kg guselkumab.

2.2.2. Clinical Studies

Guselkumab has demonstrated efficacy in psoriasis and has received marketing approval in several countries and regions globally for the treatment of adults with moderate to severe plaque psoriasis, including in the US, Canada, EU, Latin America, and the Asia Pacific region. The approved guselkumab dose for psoriasis is 100 mg by SC injection at Weeks 0, 4, and every 8 weeks (q8w) thereafter. In addition, guselkumab has been approved for the treatment of PsA, GPP, erythrodermic psoriasis, and palmoplantar pustulosis in Japan.

Guselkumab is also being studied in HS and familial adenomatous polyposis. A pediatric study in participants with chronic plaque psoriasis aged ≥6 to <18 years old is also ongoing. Phase 3 development is ongoing globally in PsA, and a seamless global Phase 2/3 clinical program is ongoing in Crohn's disease. The Phase 2b study of the ongoing Phase 2/3 guselkumab Crohn's disease program, and Phase 2 HS studies evaluated the same induction dose regimens up to a maximum dose of 1200 mg IV every 4 weeks (q4w) given 3 times, as well as a maintenance dose range from 100 mg SC q8w to 200 mg SC q4w. The ongoing Phase 3 study of the Phase 2/3 guselkumab Crohn's disease program is evaluating an induction dose of 200 mg IV q4w given 3 times and a maintenance dose of 100 mg SC q8w or 200 mg SC q4w. In addition, a guselkumab and golimumab combination Phase 2a proof-of-concept study in UC which includes a guselkumab monotherapy arm (guselkumab 200 mg IV at Weeks 0, 4, and 8 followed by guselkumab 100 mg

SC q8w) is currently ongoing. Details about these guselkumab clinical development programs across various indications are provided in Section 4 of the latest version of the guselkumab IB.

Through the IB cutoff date of 12 July 2019, an estimated 203 healthy participants, 3,454 participants with psoriasis, 109 participants with rheumatoid arthritis (RA), 1,136 participants with PsA, 182 participants with palmoplantar pustulosis, 151 participants with Crohn's disease, 149 participants with HS, 29 participants with UC, and 3 participants with familial adenomatous polyposis have been exposed to guselkumab. Overall, an estimated 5,416 participants have been exposed to guselkumab in the clinical development program.

The largest clinical experience to date with guselkumab has been in plaque psoriasis. The safety profile of guselkumab in participants with moderate to severe plaque psoriasis is based on data from the Phase 2 study CNTO1959PSO2001 and Phase 3 studies CNTO1959PSO3001, CNTO1959PSO3002, and CNTO1959PSO3003. Of the 2,177 guselkumab treated participants, 1,748 participants were exposed for at least 1 year, 1,516 were exposed for at least 2 years, and 692 participants were exposed for 3 years. Long-term extensions of 2 of the studies (CNTO1959PSO3001 and CNTO1959PSO3002) are ongoing and will continue through up to 5 years of follow-up.

2.3. Benefit-Risk Assessment

More detailed information about the known and expected benefits and risks of guselkumab may be found in the guselkumab IB.

2.3.1. Risks for Study Participation

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Clinical worsening of LN	The benefit-risk of guselkumab in treatment of LN has not been established.	• During the study, participants will be permitted to continue treatment of LN with certain standard-of-care medications (Section 6.5). • Participants may discontinue study intervention if it is not in their best interest or if they need to initiate certain protocol-prohibited medications including certain biologics (Sections 6.5 and 7.1). • Participants will be allowed to use glucocorticoids as needed, although this may trigger a TF if a high enough dose is required as detailed in Section 6.5.2.
Potential Risks Due to Study Intervention Guselkumab		
Serious infections and reactivation of latent infections	Available animal and human data suggest that blockade of IL-23 may be associated with an increased infection risk.	• Participants with a history of, or ongoing, chronic or recurrent infectious disease, including human immunodeficiency virus (HIV), Hepatitis B or C virus (HBV,

	Infections have been identified as adverse reactions of guselkumab, including respiratory infections, herpes simplex and tinea infections. and gastroenteritis.	HCV), will be excluded from the study. Similarly, participants with evidence of active or untreated latent tuberculosis (TB) will be excluded from the study (Section 5.1.1). • Participants who have received a live viral or bacterial vaccination within 12 weeks of baseline will be excluded from the study. In addition, participants must agree not to receive a live viral or live bacterial vaccination during the study and for 12 weeks after receiving the last dose of study intervention (Section 5.1.1). • Participants will be instructed to seek medical attention if they develop signs or symptoms suggestive of an infection, and investigators are instructed in the protocol to monitor for signs or symptoms of infections, including TB (Sections 8.2.10 and 8.2.11). • Discontinuation of a participant's study intervention must be strongly considered if the participant develops a serious infection, including but not limited to sepsis or pneumonia. In addition, any serious infection should be discussed with the medical monitor or designee, and study intervention should be withheld until the clinical assessment is complete (Section 7.1).
Hypersensitivity reactions, including serious hypersensitivity reactions.	Serious hypersensitivity reactions including anaphylaxis have been reported in postmarketing experience with guselkumab in psoriasis patients. Hypersensitivity, including anaphylaxis, urticaria and rash have been identified as adverse drug reactions for guselkumab.	• Participants with known allergy, hypersensitivity, or intolerance to guselkumab or its excipients will be excluded from the study. • Sites are instructed that before any administration of study intervention, appropriately trained personnel and medications (eg, injectable epinephrine) must be available to treat hypersensitivity reactions, including anaphylaxis. In addition, all participants must be observed carefully for signs and symptoms of a hypersensitivity reaction (eg, urticaria, pruritis, angioedema, wheezing, dyspnea, or hypotension) (Section 8.2.8). • Any participant who develops a serious hypersensitivity reaction such as anaphylaxis must discontinue study intervention (Section 7.1).

Malignancy	The preponderance of preclinical data suggests that blockade of endogenous IL-23 would not be detrimental and may in fact be beneficial in tumor immunosurveillance and host protection; however, a risk of malignancy cannot be excluded.	• Those participants who currently have a malignancy or have a history of malignancy within 5 years prior to screening (with exceptions noted in Section 5.1.1) will be excluded from the study. Additionally, participants who have a history of lymphoproliferative disease, including lymphoma; a history of monoclonal gammopathy of undetermined significance or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy or splenomegaly will be excluded from the study (Section 5.1.1). • During the conduct of the study, participants will undergo regular clinical monitoring including routine safety labs to assess for any changes in health status that may indicate a possible malignancy. • Participants who develop a malignancy during the study (with the exception of no more than 2 localized basal cell skin cancers that are treated with no evidence of recurrence or residual disease) will be discontinued from study intervention (Section 7.1).
Liver injury	A serious adverse event (SAE) of 'toxic hepatitis' was reported in the ongoing Phase 2/3 guselkumab Crohn's disease program in a participant who received guselkumab 1200 mg IV at Weeks 0, 4, and 8, and 200 mg SC at Week 12. Based on the hepatocellular pattern of injury, temporal relationship of the event to guselkumab exposure, and the exclusion of alternative etiologies, this event may represent drug-induced liver injury possibly related to guselkumab. Transaminase increases have been identified as an adverse reaction of guselkumab. In PsA studies transaminase increases were observed with a higher incidence with a maintenance dose of 100 mg q4w compared to100 mg q8w.	• During the conduct of the study, liver function tests will be monitored at regular intervals in accordance with regulatory guidance.[9] In addition, the induction doses in this study will be lower and will not exceed 400 mg IV. • Participants with marked liver enzyme elevations or symptoms or signs of liver dysfunction (eg, jaundice), should undergo a thorough investigation for possible causes of liver injury. A participant must have their study intervention discontinued if the participant has severe liver test abnormalities that are not transient and are not explained by other etiologies (Section 7.1).
Immunosuppression	Although guselkumab has been studied with other immunosuppressives in other diseases, there may be an increased risk of infection or malignancy.	In order to minimize the theoretical increased risk of infection or malignancy with the combination of guselkumab with immunosuppressive therapy, the

		baseline dose of oral glucocorticoids on study entry is limited to a minimum prednisone equivalent dose of 10 mg/day and maximum 1 mg/kg/day or ≤60 mg/day, whichever is lower, which must be tapered starting from Week 2. Additionally, participants are also excluded from the study if they have received oral (PO) or IV cyclophosphamide within 3 months prior to randomization, received a single B-cell targeting agent within 3 months prior to first study intervention administration; or received more than 1 previous B-cell targeting therapy including belimumab within 6 months prior to first administration of the study intervention; or received B-cell depleting therapy (eg, obinutuzumab) within 12 months prior to first administration of the study intervention or have evidence of continued B-cell depletion following such therapy: received anti-tumor necrosis factor (TNF) therapy, other biologic medications, or experimental non-biologic therapeutic agents within the past 90 day, or 5 half-lives prior to screening, whichever is greater . Further detail regarding concomitant medications is provided in Sections 5.1 and 5.1.1.
Risks Due to Study Procedures [if applicable]		
Risks associated with renal biopsy include hematuria, hematoma, and pain.	These risks are well recognized, and the risk of serious complications is rare.[33]	Trained and experienced physicians will be performing the procedure during this study.

2.3.2. Benefits for Study Participation

There is no established benefit to participants of receiving study intervention. Given the scientific rationale for IL-23 blockade in the treatment of LN (Section 2.1.2), participants may experience an improvement in disease status during treatment with guselkumab. Participants in the study will also help in furthering development of this drug to treat LN and increased understanding of LN. Thus, the knowledge gained from this study has the potential to benefit many more patients suffering with LN, and thus offers potential public health benefits.

Participants may also experience some benefit from the participation in a clinical study irrespective of receiving study treatment, due to regular visits and assessments monitoring their overall health.

2.3.3. Benefit-Risk Assessment for Study Participation

Guselkumab has undergone extensive nonclinical and clinical development as summarized in the latest version of the IB and described briefly in Section 2.2. The collective efficacy and safety results of the Phase 1, Phase 2, and Phase 3 clinical studies in healthy volunteers and patients with plaque psoriasis established a favorable benefit-risk profile for guselkumab in the treatment of plaque psoriasis and regulatory approval for the plaque psoriasis indication. In Japan, guselkumab has also been studied and received regulatory approval for the treatment of erythrodermic psoriasis, generalized pustular psoriasis, and palmoplantar pustulosis. This clinical experience provided support for the ongoing development of guselkumab in other inflammatory diseases such as Crohn's disease, UC, PsA, and HS.

Although at present there are no clinical results for guselkumab in the treatment of LN, animal and human data suggests IL-23 plays an important role in the pathogenesis of LN (Section 2.1.2) and inhibition of IL-23 cytokines will be helpful in controlling LN.

It is acknowledged that the proposed dose to be evaluated in induction (ie, 400 mg IV q4w given 3 times) and in maintenance (ie, 200 mg SC q4w) in this protocol is higher than the approved dose regimen of guselkumab in psoriasis. Based on the data from nonclinical toxicology studies (Section 2.2.1), the predicted exposure margins during the induction and maintenance treatment periods relative to the exposure at the no observed adverse effect level (NOAEL) identified in cynomolgus monkey are adequate to support the proposed clinical doses (Section 4.3). The Phase 2b study of the ongoing Phase 2/3 guselkumab Crohn's disease program and the Phase 2 HS study evaluated induction dose regimens up to 1200 mg IV. The Phase 2b/3 UC study is evaluating the same induction and maintenance dose regimens as this program. Excluding the single patient with the report of "toxic hepatitis" noted above, no significant safety concerns have been reported after treatment through up to 1 year (20 participants through 1 year and 184 through 6 months), although these Phase 2 studies evaluated a limited number of participants.

Potential risks of guselkumab, including those of serious infection and malignancy, are being addressed via judicious inclusion/exclusion criteria, frequent study visits to allow for close monitoring of patient safety, guidelines for participant management (including monitoring of clinical laboratory tests and treatment discontinuation criteria), detailed description of allowed and prohibited concomitant medications, and comprehensive medical monitoring of data by the sponsor during the conduct of the studies. In addition, a comprehensive safety monitoring plan with oversight from an external, independent Data Monitoring Committee (DMC) will be implemented to ensure the safety of guselkumab in participants with moderately to severely active LN (Section 9.5).

In summary, the collective preclinical and clinical evidence for the anti-IL-23 mechanism of action in LN, and the benefit-risk profile of guselkumab established to date in psoriasis and other immune-mediated diseases, provide a strong scientific and clinical rationale for pursuing development of guselkumab in patients with active LN and for the investigation of guselkumab in this Phase 2 program. Taking into account the measures taken to minimize risk to participants in this study, the potential risks associated with guselkumab are justified by the potential benefits that may be provided to participants with LN.

3. OBJECTIVES AND ENDPOINTS

Due to the Sponsor's decision to terminate the study early, only the primary endpoint, major secondary endpoints and safety endpoints may be reported in the clinical study report. Details will be described in the statistical analysis plan (SAP).

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 LN	• **Primary endpoint**: Proportion of participants achieving at least 50% decrease in proteinuria from baseline at Week 24 • **Major 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 • Proportion of participants with UPCR <0.75 mg/mg at Week 24 • Time to achievement of CRR • Time to 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 60, end of long-term extension (LTE), and in participants discontinuing study intervention early

Objectives	Endpoints
Tertiary/Exploratory	
• To evaluate the efficacy of guselkumab in participants with active LN over an extended period	• Proportion of participants maintaining CRR at Week 152
• 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 • Changes in PRO assessments including LupusQOL, FACIT-Fatigue, lupus symptoms, and PGIC over time during the long-term extension
• 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 [IFN]-gamma, chemokines), and/or tissue gene expression

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

Definitions of Efficacy Endpoints:

- **At least 50% decrease in proteinuria from baseline**

  Participants who have a decrease in proteinuria of at least 50% from baseline based on UPCR.

- **Sustained reduction in steroid dose ≤10 mg/day of prednisone or equivalent**

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

- **Complete renal response**

  Urine Protein to Creatinine Ratio (UPCR) <0.5 mg/mg.

  AND

  Estimated Glomerular Filtration Rate (eGFR) ≥60 mL/min/1.73m^2 or no confirmed decrease ≥20% from baseline.

  AND

  Prednisone dose ≤10 mg/d.

- **Time to achievement of complete renal response**

  Time to first observation of CRR from baseline.

- **Time to Treatment Failure**

  Time to first occurrence of TF from baseline (Section 9.4.2).

- **Four (4) points improvement in systemic lupus erythematosus disease activity index 2000 modified to exclude renal items**

  A 4-point improvement from baseline in total SLEDAI-2K score modified to exclude renal items (i.e., urinary casts, hematuria, proteinuria, pyuria).

- **50% reduction in active joints**

  Participants with baseline arthritis (with at least 4 active joints at baseline) and a ≥50% reduction in active joints from baseline, i.e., an active 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.

- **50% reduction in Cutaneous Lupus Erythematosus Disease Area and Severity Index score**

  Participants with baseline active mucocutaneous lupus manifestations (CLASI ≥8) and ≥50% reduction in CLASI score from baseline (CLASI Activity and CLASI Damage analyzed independently).

HYPOTHESIS

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 achieving at least a 50% reduction of proteinuria with protocol specified steroid tapering regimen at Week 24.

4. STUDY DESIGN

4.1. Overall Design

4.1.1. Main Study

This is a randomized, double-blind, placebo-controlled, parallel, multicenter, interventional Phase 2 study in participants aged 18 to 75 (inclusive) with active LN. The total duration of the original study was 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 MMF/MPA at/or within 2 weeks of screening may extend screening for up to 4 additional weeks.

Unscheduled visits are permitted for reasons such as safety events or worsening of LN.

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. After all enrolled participants have completed the Week 20 visit, no additional study intervention will be administered. For further details of end of study, see Section 4.1.3.

A placebo comparator (in addition to standard-of-care background therapy) will be used in this study through Week 48 to allow for blinded, placebo-controlled evaluation of the long-term efficacy and safety of guselkumab in participants with LN. Participants will be stratified by geographic region and UPCR level.

Efficacy, safety, PK, immunogenicity, and biomarkers (where local regulations permit) will be assessed according to the Schedule of Activities (SoA; Section 1.3). 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 (see Section 6.5.2 for information on glucocorticoid tapering). 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 (TB).

Participants who complete the Week 52 visit and achieve a complete renal response, may have the option to participate in an LTE study; see Section 4.1.2 for further details.

Participants who experience an LN flare during the main study will be discontinued from study intervention. An LN flare is defined as an increase in proteinuria and/or serum creatinine concentration, abnormal urine sediment or a reduction in creatinine clearance rate as a result of active disease requiring a change in an immunomodulatory medication for LN beyond that which is outlined in Section 6.5.

An external, independent DMC will be commissioned for this study (Section 9.5). 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.

A diagram of the study design is provided in Section 1.2, Schema.

4.1.2. Long-Term Extension

Participants who complete the assessments at the Week 52 visit and have achieved CRR may have the option to participate in the LTE of the study. The LTE begins after the assessments have been completed at Week 52. The objective of the LTE is to evaluate the efficacy and safety of long-term guselkumab treatment.

If a participant has achieved CRR at Week 48, they will be considered potentially eligible for the LTE. At Week 52, after the assessments per the SoA have been completed and informed consent for the LTE has been confirmed, the participant will receive the study intervention that was assigned at randomization. Participants will continue to receive the same study intervention every 4 weeks during the LTE that they were assigned to receive through Week 48. The Week 52 assessments will be checked after this visit to confirm that the participant has still achieved CRR. If the participant has not achieved CRR at Week 52, study intervention will be discontinued, and the participant will be required to complete the final efficacy and safety visits approximately 12 weeks after their last study intervention administration.

At the discretion of the investigator and participant, and after appropriate and documented training, participants may self-administer study intervention at home during the LTE for the visits specified in the SoA. A caregiver may also be trained to administer study intervention. After receiving training at Week 60, participants who are eligible for self- (or caregiver) administration of study intervention will be supplied with study intervention for at-home administration and may have their first at-home administration at Week 64. Participants will record all at-home study intervention administrations on a diary card. Participants will also be instructed to contact the investigator promptly in the event of any signs of an allergic reaction, infection, or malignancy.

Finally, participants will continue to have study visits at the investigative sites approximately q8w through Week 148 and assessments performed as outlined in Section 1.3.

Participants who are unable or unwilling to have study intervention administered away from the investigative site will continue administration at the investigative site and will be required to return to the site for administration of study intervention.

During the LTE, all participants will be assessed for safety and efficacy. Participants who experience an LN flare during the LTE will be discontinued from study intervention and will be required to complete the final efficacy/safety visits. An LN flare is defined as an increase in proteinuria and/or serum creatinine concentration, abnormal urine sediment or a reduction in creatinine clearance rate as a result of active disease requiring a change in an immunomodulatory medication for LN beyond that which is outlined in Section 6.5. Every effort should be made to continue to adhere to the requirements for concomitant and prohibited therapy as outlined in Section 6.5 of the protocol with some exceptions for antimalarials, angiotensin-converting enzyme (ACE) inhibitors/ angiotensin II receptor blockers (ARBs), and glucocorticoids; see Section 6.5 for further details.

All study evaluations that should be performed during the LTE are listed in the SoA (Table 2 and Table 3).

The study blind will be maintained throughout the study (including the LTE).

One database lock (DBL) for the study will occur at the end of study.

4.1.3. 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 Schedule of Activities (Section 1.3).

4.2. Scientific Rationale for Study Design

A double-blind, placebo-controlled study was selected where guselkumab or placebo would be randomized in addition to standard-of-care background therapy. This study design was selected as a true placebo comparator group is unethical for this serious disease condition. Therefore, placebo and experimental treatments will be added to a standard-of-care regimen of MMF/MPA and glucocorticoids.

With this standard-of-care regimen, participants will enter on glucocorticoids (at minimum prednisone equivalent dose of 10 mg/day and not exceeding 1 mg/kg/day or 60 mg/day prednisone or its equivalent, whichever is lower) and will be tapered fairly rapidly to 5 mg/day prednisone equivalent by Week 12 to minimize confounding treatment effects of glucocorticoids on major efficacy endpoints, as has occurred in several, negative LN studies.[14] Similar glucocorticoid tapers have been used in some recent LN studies.[31]

For participants who will be treated with guselkumab, an IV induction dose of guselkumab initially through Week 12 was chosen, followed by SC doses as this follows the typical induction-maintenance treatment paradigm for Class III/IV LN. This ensures target inhibition of IL-23 in the kidney in this proof-of-relevance study. This dose of guselkumab is also being evaluated in a Phase 2b/3 study in UC. Additional details are described in Section 4.3.

A primary analysis at Week 24 will be conducted for proof-of-concept and to allow for Phase 3 LN program planning.

4.2.1. Blinding, Control, Study Phase/Periods, Intervention Groups

Randomization will be used to minimize bias in the assignment of participants to intervention groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention groups. Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

4.2.2. DNA and Biomarker Collection

Biomarker samples (where local regulations permit) will be collected to evaluate the cellular and molecular mechanism of action of guselkumab, or help to explain interindividual variability in clinical outcomes, or to identify population subgroups that respond differently to an intervention. Biomarkers will be analyzed from the serum, as well as urine, in participants from select sites to assess PD markers associated with the IL-23 pathway, and with response to guselkumab. Whole blood samples will be collected from participants to assess the effect of study intervention on ribonucleic acid (RNA) expression profiles, where local regulations permit. The goal of the biomarker analyses is to further define the mechanism of action of the selective blockade of IL-23 with guselkumab in LN and aid in evaluating the intervention-clinical response relationship. Biomarker samples may also be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies for lupus.

Optional pharmacogenomic samples may be obtained. It is recognized that genetic variation can be an important contributory factor to interindividual differences in intervention distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes, identify markers associated with disease susceptibility and prognosis, and may help to identify population subgroups that respond differently to an intervention. The goal of the pharmacogenomic component is to collect DNA to allow for the identification of genetic factors that may influence the PK, PD, efficacy, safety, or tolerability of guselkumab and to identify genetic factors associated with LN or the response to guselkumab treatment. The focus of this analysis will be the evaluation of genetic single nucleic polymorphisms (SNP) associated with LN and response to treatment with guselkumab. No genetic research will be done on samples from participants unless specific consent is provided by signing the optional genetic research informed consent form (ICF). Additional pharmacogenomic samples will be collected after exposure to guselkumab or placebo. Epigenetic data from these samples will be compared to baseline collected samples to identify epigenetic changes that may associate with treatment or treatment response.

Collection of biomarker samples, including samples from the optional pharmacogenomic collection, will only occur where local regulations permit and may not occur at all clinical sites.

4.2.3. Participant Input Into Design

Two advisory boards of LN patients were consulted on the study design and conduct. Participants provided insights on the protocol design, where they perceived barriers to participation, and how the clinical study experience could be improved for patients. In particular, concerns were raised about some of the inclusion/exclusion criteria (biopsy requirement, steroid tapering) and the SoA, as some additional biomarker and actigraphy assessments were being considered at that time.

New recruitment strategies were identified, including: providing sites with tools to help identify newly diagnosed patients in their referral network that could be a good fit for the study, providing more information about the biopsy requirement to explain its significance to potential participants, and providing more education to potential participants about the protocol design and the protections in place for participants of clinical trials.

4.2.4. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The primary ethical concern is the medication has not been shown to have efficacy in humans and response to medication is theoretical at this time.

The total blood volume to be collected from each participant in this study is less than the American Red Cross standard limit for whole blood donation (approximately 475 mL q8w) and is, therefore, considered an acceptable amount of blood to be collected over this time. For more details regarding blood collection, see Blood Sample Collection in Section 8.

4.3. Justification for Dose

The guselkumab dose regimen was selected based on the objective of determining the maximum efficacy of guselkumab possible for treatment of LN, the existing safety information from relevant preclinical and clinical studies, the approved dose regimen for psoriasis, and the understanding of similar dosing requirements for induction and maintenance therapy in LN (and SLE) and Crohn's disease.

As the objective of this study is to demonstrate proof-of-concept for efficacy of guselkumab in the treatment of LN, the maximum practicable dose (400 mg IV at Week 0, 4, and 8 then followed by 200 mg SC q4w), is chosen to be evaluated.

Data from the ongoing guselkumab Phase 2/3 Crohn's disease program were considered in the selection of the guselkumab IV induction dose regimens in this Phase 2 LN study. In the Phase 2

Crohn's disease study, 3 guselkumab IV induction doses of 200 mg, 600 mg and 1200 mg IV q4w were assessed. CCI [redacted]

The safety of 200 mg and 600 mg IV regimens in the Phase 2b Crohn's disease trial was acceptable. A single case of potential drug-induced liver injury possibly related to guselkumab was reported in a participant who received the guselkumab 1200 mg IV dose regimen. Compared to the guselkumab 1200 mg IV dose, the guselkumab 400 mg IV dose would provide an approximately 3-fold lower exposure. In addition, the predicted exposure margin for 400 mg IV relative to the NOAEL of 50 mg/kg/week in cynomolgus monkeys is approximately 10 to 13-fold (Table 4), which is considered adequate to support the limited duration of IV dosing (ie, 3 doses over 12 weeks).

The proposed dose regimen is supported by safety margins from preclinical toxicology data as well as clinical safety data of guselkumab in other disease populations such as psoriasis, PsA, Crohn's disease, UC, and HS. Guselkumab IV doses of up to 50 mg/kg weekly for 5 weeks, and guselkumab SC doses of up to 50 mg/kg weekly for 24 weeks, were well-tolerated in cynomolgus monkeys. The predicted human guselkumab exposures following the proposed IV and SC dosages generate acceptable safety margins. Shown in Table 4, the estimated safety margins are approximately 10-to 13-fold for the 400 mg IV dosing and 30-to 40-fold for 200 mg SC q4w dosing.

Table 4: Guselkumab Predicted Exposure Margins

Guselkumab Predicted Exposure Margins at 400 mg IV Induction Dosing		
Parameters	**Mean C_{max} (µg/mL)**	**Mean AUC (µg.day/mL)**
Cynomolgus Monkey Exposure at the NOAEL (50 mg/kg/week) Following 4 Weekly IV Doses	1432[a]	4817[b]
Human Predicted IV Exposure	109[c]	497[d]
Predicted Exposure Margin[e]	*13.1*	*9.7*
Guselkumab Predicted Exposure Margins at 200 mg SC Maintenance Dosing		
Parameters	**Mean C_{max} (µg/mL)**	**Mean AUC (µg.day/mL)**
Cynomolgus Monkey Exposure at the NOAEL (50 mg/kg/week) Following 24 Weekly SC Doses	993[a]	5412[b]
Human Predicted SC Exposure	30[c]	134[d]
Predicted Exposure Margin[e]	33.1	40.4

Abbreviations: AUC area under the curve; C_{max} maximum serum concentration; IV intravenous; NOAEL no observed adverse effect level; SC subcutaneous

a. Highest observed concentration following the fourth 50 mg/kg dose (IV) or the twenty fourth 50 mg/kg dose (SC)
b. For IV, AUC from Day 21 through 28 (1 week after the last 50 mg/kg dose); or for SC, AUC from Day 161 through 168 (1 week after the last 50 mg/kg dose).
c. Highest predicted concentration after the third 400 mg IV guselkumab dose, or at steady state following SC administration.
d. Predicted human AUC after the third 400 mg IV guselkumab dose (from Week 8 through Week 12), or at steady state following 200 mg SC every 4 weeks administration. Each value was divided by 4 to obtain the AUC over one week, which in

Table 4: Guselkumab Predicted Exposure Margins

Guselkumab Predicted Exposure Margins at 400 mg IV Induction Dosing

turn corresponds to the AUC interval for cynomolgus monkeys. Simulation of human PK exposure was based on a body weight of 70 kg.

e. Exposure margins represent the ratio between guselkumab exposure metrics in the cynomolgus monkey compared with those predicted in humans.

In study CNTO1275SLE2001 (ClinicalTrials.gov Identifier: NCT02349061), the studied Crohn's disease dose regimen (~6 mg/kg IV followed by 90 mg SC q8w) for ustekinumab, an antibody targeting at IL-12/IL-23, demonstrated efficacy in SLE participants. Similar ustekinumab PK exposures have been demonstrated in participants with SLE and participants with Crohn's disease following the same dosage.

The proposed induction dosing followed by maintenance paradigm is a characteristic for management of LN, as well as Crohn's disease and UC. Induction therapy is essential to control and reduce renal damage and the maintenance therapy is important to prevent renal flares.[5]

Overall, with an acceptable NOAEL, available clinical safety data from other ongoing studies in conjunction with other similarities between SLE and Crohn's disease in the ustekinumab studies (in terms of induction dosing, efficacy, and PK), make it reasonable to study LN, a severe manifestation of SLE, with this regimen.

4.4. End of Study Definition

End of Study Definition

The end of the study is defined as the last follow-up assessment for the last participant in the study (see Section 4.1.3 for further details). The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement.

Study Completion Definition

A participant will be considered to have completed the main study if he or she has completed assessments through Week 52 and the 12-week safety follow-up visit or has completed the assessments through Week 52 and enters the LTE. A participant will be considered to have completed the full study if he or she has completed assessments through Week 152 and the 12-week safety follow-up visit.

5. STUDY POPULATION

Screening for eligible participants will be performed within 8 weeks before administration of the study intervention. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures are allowed.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed. The inclusion and exclusion criteria will be adjudicated prior to enrollment. The

adjudicated assessment by the sponsor or designee will be the final determinant for allowing enrollment.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2, Sample Size Determination.

5.1. Main Study Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. Male or female (according to their reproductive organs and functions assigned by chromosomal complement).

2. 18 to 75 years of age, inclusive.

3. Meets classification criteria for SLE by the 2019 European League Against Rheumatism (EULAR)/ACR.

4. Criterion modified per Amendment 3.

   4.1. Kidney biopsy documentation of active ISN/RPS proliferative nephritis: Class III-IV (with or without class V membranous nephritis) within the last 6 months prior to screening or performed during screening.

Concomitant or previous medical therapies received

5. Criterion modified per Amendment 3.

   5.1. Must have received MMF or MPA for at least 8 weeks at the time of randomization, and currently receiving MMF at a dose of ≤3 g/day or MPA at dose of ≤2.2 g/day.

   Note: Screening may be extended by up to 4 additional weeks for participants who start MMF/MPA at or near (within 2 weeks before) the beginning of screening to allow for repeat of laboratory entry criteria after 8 weeks of MMF/MPA treatment.

6. Criterion modified per Amendment 3.

   6.1. At screening and randomization, must be receiving oral glucocorticoids at minimum prednisone equivalent dose of 10 mg/day and maximum 1 mg/kg/day or ≤60 mg/day, whichever is lower. Treated for ≥6 weeks with stable dosing ≥2 weeks before randomization.

7. If receiving angiotensin-converting enzyme (ACE) inhibitor/angiotensin II receptor blockers (ARB), a stable dose for at least 2 weeks prior to randomization.

8. If using antimalarials, must have been treated for ≥12 weeks, and with stable dosing for ≥6 weeks at time of randomization. See Table 5 for permitted dosing levels.

Screening laboratory tests

9. Criterion modified per Amendment 3.

   9.1. Positive antinuclear antibody (ANA; ≥1:80 titer by central laboratory test) or anti-dsDNA antibodies (≥30 IU/mL by central laboratory test) detected at screening.

10. UPCR ≥1.0 mg/mg assessed on 2 first morning urine void specimens during screening. Note: These 2 specimens do not need to be on consecutive days, however, 2 samples must be tested with UPCR ≥1.0 mg/mg in a row. The UPCR requirement must be met after at least 8 weeks of MMF/MPA treatment, and after stable glucocorticoid dosing is achieved at the dose intended at time of randomization.

Tuberculosis: The participant is considered eligible according to the following TB screening criteria in Inclusion #11 to 14:

11. Has no history of latent or active TB before screening. An exception is made for participants who have a history of latent TB AND satisfy one of the following criteria:

    a. are currently receiving treatment for latent TB

       OR

    b. will initiate treatment for latent TB before the first dose of study intervention

       OR

    c. have documentation of having completed appropriate treatment for latent TB within 5 years before the first dose of study intervention. It is the responsibility of the investigator to verify the adequacy of previous anti-tuberculous treatment and provide appropriate documentation. Patients with a history and documentation of having completed appropriate treatment for latent TB more than 5 years before the first dose of study intervention are not eligible.

12. Has no signs or symptoms suggestive of active TB based on medical history and/or physical examination.

13. Has had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB before the first dose of study intervention.

14. Within 8 weeks prior to the first dose of study intervention, have a negative QuantiFERON-TB® test result, or have a newly identified positive QuantiFERON-TB® test in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated prior to the first dose of study intervention (see Section 8.2.11). Indeterminate or borderline results should have the test repeated as described in Section 8.2.11.

    Note: A negative tuberculin skin test result (see Appendix 3 [Section 10.3]) is additionally required if the QuantiFERON-TB® test is not approved/registered in the country in which this protocol is being conducted. In Ukraine, while the QuantiFERON-TB® test is not approved/registered, it is acceptable, and an additional tuberculin skin test is not required. The QuantiFERON-TB® test and the tuberculin

skin test are not required at screening for participants with a history of latent TB, if active TB has been ruled out, and if appropriate treatment has been initiated/completed as described above in Inclusion Criterion #11.

Has a chest radiograph (both posterior-anterior and lateral views, or per country regulations where applicable), taken within 12 weeks prior to randomization and read by a qualified radiologist (or pulmonologist in accordance with local regulations), with no evidence of current, active TB or old, inactive TB. A chest computed tomography (CT) scan is also acceptable if obtained instead of a chest radiograph outside of the protocol.

Contraception

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

15. A woman of childbearing potential must have a negative urine pregnancy test at screening and at Week 0.

16. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 12 weeks after the last dose of study intervention.

17. Criterion modified per Amendment 2.

    17.1. Before randomization, a woman must be (as defined in Appendix 5 [Section 10.5], Contraceptive and Barrier Guidance and Collection of Pregnancy Information):

    a. Not of childbearing potential

    OR

    b. Of childbearing potential and:

    - If heterosexually active, practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study intervention and until 12 weeks after last dose (ie, the end of relevant systemic exposure). Examples of highly effective methods of contraception are located in Appendix 5 (Section 10.5), Contraceptive and Barrier Guidance and Collection of Pregnancy Information; however, the method selected must meet local/regional regulations/guidelines for highly effective contraception.
    - If using oral hormonal contraceptives for birth control and receiving MMF/MPA, a woman must, in addition to the oral hormonal contraceptive, utilize a barrier method of birth control (eg, either an occlusive cap [diaphragm or cervical/vault caps] plus spermicidal

foam/gel/film/cream/suppository if available in their locale) or their partner must agree to use a condom with spermicidal foam/gel/film/cream/suppository if available in their locale, during the study and for at least 30 days after receiving the last administration of study intervention.

Note: If a participant's childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin using a highly effective method of contraception, as described above.

18. A man who is sexually active with a woman of childbearing potential and who has not had a vasectomy must agree to use a barrier method of birth control, eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

19. A male participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum of 12 weeks after receiving the last dose of study intervention.

General

20. Must sign an ICF indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study. (In regions where the legal age of consent is older than 18 years, those under the legal age, must obtain signed informed consent from both the participant and his or her legally acceptable representative.)

21. Must sign a separate ICF if he or she agrees to provide optional DNA samples for research where local regulations permit. In regions where the legal age of consent is older than 18 years, those under the legal age, must obtain signed informed consent from both the participant and his or her legally acceptable representative.
Refusal to give consent for the optional DNA samples does not exclude a participant from participation in the study.

22. Must be willing and able to adhere to all specified requirements, including but not limited to completion of the required assessments, adherence to the visit schedule, and compliance with the lifestyle restrictions as specified in this protocol.

23. Must be able to read and write.

5.1.1. Long-Term Extension Inclusion Criteria

Each potential participant must satisfy the following criteria to continue to receive study intervention as part of the LTE:

1. The participant has achieved CRR at Weeks 48 and 52 and has completed the Week 52 assessments per Table 2 of the SoA (Section 1.3).

2. Must sign an ICF indicating that he or she understands the purpose of, and procedures required for, the LTE and is willing to participate in the LTE. (In regions where the legal age of consent is older than 18 years, those under the legal age, must obtain signed informed consent from both the participant and his or her legally acceptable representative.)

3. In the judgement of the study Investigator, the participant must be suitable for inclusion in the LTE portion of the study.

5.2. Main Study Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. Current or history of, severe, progressive, or uncontrolled renal disease, with the exception of active LN.

2. Current or history of, severe, progressive, or uncontrolled hepatic, hematological, gastrointestinal, pulmonary, cardiac, or neurological disease, either related or unrelated to SLE (or, in the investigator's opinion, any other concomitant medical condition that places the participant at risk by participating in this study).

3. Anticipated to require dialysis within 6 months.

4. Transplanted organ (with the exception of a corneal transplant performed >12 weeks before screening).

5. Comorbidities (other than LN, eg, asthma, chronic obstructive pulmonary disease) which have required 3 or more courses of systemic glucocorticoids within the previous 12 months.

6. Has any unstable or progressive manifestation of SLE (eg, lupus cerebritis, optic neuritis, transverse myelitis, psychosis, uncontrolled seizures, systemic vasculitis, rapidly progressive glomerulonephritis, end-stage renal disease], pulmonary hemorrhage, myocarditis) that is likely to warrant escalation in therapy beyond permitted background medications. Participants requiring renal hemodialysis or peritoneal dialysis are also excluded.

7. Criterion modified per Amendment 3.

   7.1. Isolated or predominant Class V LN (ie, without coexistent Class III or IV nephritis).

8. Has other inflammatory diseases that might confound the evaluations of efficacy, including but not limited to RA, PsA, RA/lupus overlap, psoriasis, Crohn's disease, or active Lyme disease.

9. Has a history or suspected occurrence of drug-induced lupus.

10. Has a history of catastrophic antiphospholipid syndrome (APS). Subjects with a history of non-catastrophic APS must be adequately controlled with anticoagulation and/or anti-platelet therapy in accordance with local guidelines. The suitability of the subject to participate in the study must be discussed with the medical monitor and/or sponsor before the subject is randomized.

11. Has inherited complement deficiency or combined variable immunodeficiency.

Screening laboratory tests

12. eGFR <30 ml/min per 1.73m^2.

13. Absolute neutrophil count <1.0 $\times 10^9$/L.

14. Platelet count <75 $\times 10^9$/L.

15. Criterion modified per Amendment 1.

    15.1 Hemoglobin <8.0 g/dL.

16. Liver function test (aspartate aminotransferase [AST], alanine aminotransferase [ALT]) results that are ≥3× the upper limit of normal [ULN]).

Concomitant or previous medical therapies received

17. Previously treated with anti-IL-23 or anti-IL-12/23 therapy.

18. Have received a single B-cell targeting agent within 3 months prior to randomization; or received more than 1 previous B-cell targeting therapy including belimumab within 6 months prior to randomization; or received B-cell depleting therapy (eg, rituximab, obinutuzumab) within 12 months prior to randomization or has evidence of continued B-cell depletion following such therapy.

19. Criterion modified per Amendment 3.

    19.1. Received PO or IV cyclophosphamide within 3 months prior to randomization.

20. Use of anti-TNF medication, other biologic medications (eg, tocilizumab, alefacept, efalizumab, natalizumab, abatacept, anakinra, brodalumab, secukinumab, ixekizumab, or agents whose mechanism of action targets IL-1, IL-2, IL-6, IL-17, or CTLA-4), or

experimental non-biologic therapeutic agents within the past 90 days, or 5 half-lives prior to screening, whichever is greater.

21. Intravenous immunoglobulin, plasmapheresis, or leukopheresis within 90 days of screening.

22. Use of investigational biologic agent within 3 months or 5 half-lives prior to screening.

23. Criterion modified per Amendment 3.

23.1. Has received systemic immunomodulatory agents (eg, leflunomide, methotrexate [MTX], tacrolimus, sirolimus, mizoribine, cyclosporine, voclosporin) other than those described in inclusion criteria #5 to #8 within 3 months (2 months for azathioprine [AZA]/6-mercaptopurine [6-MP]) prior to randomization (Section 6.5.7). Glucocorticoids are not included in this criterion; see Section 6.5.2 regarding glucocorticoid use.

24. Has received adrenocorticotropic hormone (ACTH) administered by injection within 1 month prior to randomization.

25. Has received topical cream/ointment preparations of cyclosporine A, high potency topical glucocorticoids (World Health Organization WHO Classification, Group I to III), or other topical immunomodulatory agents (such as tacrolimus, pimecrolimus) within 4 weeks prior to randomization covering a body surface area (BSA) of >20%.

26. Is currently receiving venom immunotherapy (honeybee, wasp, yellow jacket, hornet, or fire ant).

27. Criterion modified per Amendment 3.

27.1. Has received epidural, IV, or IM administration of glucocorticoids at a prednisone equivalent dose of >125 mg/day within 6 weeks prior to randomization.

28. Criterion modified per Amendment 3.

28.1. The participant is anticipated to receive >125 mg/day of intravenous prednisone (or equivalent) during the screening period.

Note: This includes the extended screening period for participants starting MMF/MPA at or near the beginning (within 2 weeks) of screening.

29. Use of complementary therapies, including traditional/Chinese medicines, herbs, ointments, or procedures (eg, acupuncture), that have the potential to activate (eg, echinacea) or inhibit (eg, *Tripterygium wilfordii* Hook F) the immune system is prohibited within 6 weeks of randomization. In addition, use of complementary therapies, including traditional/Chinese medicines and herbs, that have the potential to interact with antithrombotic agents (eg, St. John's Wort) is prohibited within 6 weeks of randomization in those taking antithrombotic agents. Any questions or concerns with the use of these therapies should be discussed with the study sponsor and/or medical monitor.

Infections or predisposition to infections

NOTE: For COVID-19-related exclusion, see exclusion criterion 56.

30. History of latent or active granulomatous infection, including histoplasmosis or coccidioidomycosis, before screening. Refer to Inclusion Criteria #11 to 14 for information regarding eligibility with a history of latent TB.

31. History of, or ongoing, chronic or recurrent infectious disease, including but not limited to, recurrent sinopulmonary infections, bronchiectasis, recurrent renal/urinary tract infection (eg, recurrent pyelonephritis, recurrent cystitis), an open, draining, or infected skin wound, or an ulcer.

32. Chest radiograph within 12 weeks before randomization that shows an abnormality suggestive of a malignancy or current active infection, including TB.

33. History of being HIV antibody-positive, or tests positive for HIV at screening.

34. Is seropositive for antibodies to HCV, unless they satisfy 1 of the following conditions:

    a. Has a history of successful treatment, defined as being negative for HCV RNA at least 24 weeks after completing antiviral treatment, and has a negative HCV RNA test result at screening,

    OR

    b. While seropositive, has a negative HCV RNA test result at least 24 weeks prior to screening and a negative HCV RNA test at the screening.

35. Tests positive for HBV infection, see (Appendix 4 [Section 10.4]).

    Note: For participants who are not eligible for this study due to HIV, HCV, and HBV test results, consultation with a physician with expertise in the treatment of those infections is recommended.

36. Bacille Calmette-guérin (BCG) vaccination within 12 months or any other live bacterial or live viral vaccination within 12 weeks of randomization.

37. Has or has had a nontuberculous mycobacterial infection or clinically significant opportunistic infection (eg, cytomegalovirus colitis, pneumocystosis, invasive aspergillosis).

38. Has a history of an infected joint prosthesis, or has ever received antibiotics for a suspected infection of a joint prosthesis, if that prosthesis has not been removed or replaced.

39. Has had a clinically significant infection (eg, hepatitis, sepsis, pneumonia, pyelonephritis), has been hospitalized for an infection, or has been treated with parenteral antibiotics for an infection within 2 months before randomization. Treated and resolved infections not considered clinically significant at the discretion of the investigator need not be exclusionary (eg, acute upper respiratory tract infection, uncomplicated urinary tract infection).

40. Evidence of a herpes zoster infection within 8 weeks of randomization. Past history of disseminated or central nervous system herpes zoster would be exclusionary.

Malignancy or increased potential for malignancy

41. Currently has a malignancy or has a history of malignancy within 5 years before screening (with the exception of a nonmelanoma skin cancer that has been adequately treated with no evidence of recurrence for at least 3 months [defined as a minimum of 12 weeks] before randomization or cervical carcinoma in situ that has been treated with no evidence of recurrence for at least 3 months before randomization).

42. History of lymphoproliferative disease, including lymphoma; a history of monoclonal gammopathy of undetermined significance; or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy or splenomegaly, or other precancerous lesions (except those of the skin such as actinic keratosis).

Coexisting medical conditions or past medical history

43. Has unstable suicidal ideation or suicidal behavior in the last 6 months, that may be defined as an electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) rating at screening of:

- Ideation level 4: Some intent to act, no plan; OR
- Ideation level 5: Specific plan and intent; OR
- Any of the following suicidal behaviors:

  Actual suicide attempts

  Interrupted attempts

  Aborted attempts

Preparatory actions

AND

is confirmed to be at risk by the investigator based on an evaluation by a mental health professional. The final decision on excluding a participant will be made at the judgment of the investigator.

44. Poor tolerability of venipuncture or lacks adequate venous access for required blood sample collections during the study period.

45. History of drug or alcohol abuse according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition , within 1 year before screening.

46. Known allergy, hypersensitivity, or intolerance to guselkumab or its excipients (refer to the guselkumab IB).

47. Known intolerance to MMF or MPA.

48. Has shown a previous immediate hypersensitivity response, including anaphylaxis, to mAbs.

49. Is a woman who is pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study or within 12 weeks after the last dose of study intervention.

50. Is a man who plans to father a child while enrolled in this study or within 12 weeks after the last dose of study intervention.

51. Has had major surgery (eg, requiring general anesthesia and hospitalization) within 8 weeks before screening, or will not have fully recovered from such surgery, or has such major surgery planned during the time the participant is expected to participate in the study.

    Note: Participants with planned surgical procedures to be conducted under local anesthesia may participate.

52. Has undergone a splenectomy.

General

53. Lives in an institution on court or authority order.

54. Currently participating or intends to participate in any other study using an investigational agent or procedure during the conduct of this study.

55. Is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

56. Criterion modified per Amendment 2.

56.1 A potential participant with the following features will be excluded from participating in the study protocol:

During the 6 weeks prior to baseline, have had ANY of (a) confirmed SARS-CoV-2 (Coronavirus Disease 2019; COVID-19) infection (test positive), OR (b) suspected SARS-CoV-2 infection (clinical features without documented test results), OR (c) close contact with a person with known or suspected SARS-CoV-2 infection

- Exception: may be included with a documented negative result for a validated SARS-CoV-2 test

(i) obtained at least 2 weeks after conditions (a), (b), (c) above (timed from resolution of key clinical features if present, eg, fever, cough, dyspnea)

AND

(ii) with absence of ALL conditions (a), (b), (c) above during the period between the negative test result and the baseline study visit

- NOTES on COVID-related exclusion:
  1. The field of COVID-related testing (for presence of, and immunity to, the SARS-CoV-2 virus) is rapidly evolving. Additional testing may be performed as part of screening and/or during the study if deemed necessary by the investigator and in accordance with current regulations/guidance from authorities/standards of care.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.4, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Appendix 9, [Section 10.9] Regulatory, Ethical, and Study Oversight Considerations. The sponsor's or designee's decision, as determined by adjudication of inclusion and exclusion criteria, is the final determinant for eligibility to participate in the study.

5.2.1. Long-Term Extension Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the LTE. If there are questions, the site should contact the sponsor for clarification.

1. The participant experiences an LN flare as defined in Section 4.1.1.

2. The participant should not have permanently discontinued study intervention or met criteria for discontinuation of study intervention.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study including the LTE to be eligible for participation:

1. Refer to Section 6.5, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the inclusion and exclusion criteria (eg, contraceptive requirements).

3. Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Participants should continue using these contraceptive measures for 12 weeks after last dose of study intervention.

4. Must agree not to receive a live virus or live bacterial vaccination during the study and for 12 weeks after receiving the last dose of study intervention.

5. Must agree not to receive a BCG vaccination during the study and for 12 months after receiving the last dose of study intervention.

6. Participants who require treatment for latent TB must complete the appropriate course of TB therapy as described in Section 5.1, Inclusion Criteria.

7. Must not receive guselkumab outside of this protocol or participate in any other clinical study with an investigational agent while in this study and must terminate study participation if they do. A participant who intends to participate in any other clinical study with an investigational agent should complete the appropriate visit(s) as described in Section 1.3 before he or she terminates study participation.

8. Agree to avoid excess exposure to natural or artificial (tanning beds, phototherapy, etc) sunlight. In addition, it is advised that subjects maintain their typical use of sun protective measures (such as a hat, sunglasses, protective clothing, sunscreen). The time period for this requirement is from the start of screening until the last dose of study agent has been received.

9. Participants who are entering the LTE and self-administering the study intervention at home must be willing and able to complete a diary card to document clinical symptoms, AEs, etc.

10. It is recommended participants be up-to-date on all age-appropriate vaccinations prior to screening per routine local medical guidelines. For study participants who received locally approved (including emergency use-authorized) COVID-19 vaccines recently prior to study entry, follow applicable local vaccine labelling, guidelines, and standards of care for patients receiving immune-targeted therapy when determining an appropriate interval between vaccination and study enrollment (see also Section 6.5.9).

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened one time after discussion with the sponsor representative.

Rescreening

Rescreened participants will be assigned a new participant number, undergo the informed consent process, and then start a new screening phase. Some assessments from screening (eg, hepatitis B virus, hepatitis C virus, HIV, chest x-ray, ANA, flow cytometry) could be considered to be complete without repeating for rescreening after discussion and written agreement by the sponsor or sponsor representative.

Rescreening of participants after the sponsor's decision to stop screening of new participants is not permitted.

Retesting

Retesting of abnormal laboratory values that may lead to exclusion will be allowed once. Retesting can occur at an unscheduled visit during the screening phase, as long as this is done within the specified screening window of up to 8 weeks (with 4 additional weeks for those who qualify per MMF start date as noted above). If a laboratory abnormality occurs, the site is encouraged to wait for all laboratory tests to be completed to ensure other laboratory tests do not need to be repeated, as only 1 retest of laboratory tests is allowed. A screening laboratory test(s) analyzed by the central

laboratory may be repeated more than once in the event of suspected error in sample collection or analysis as long as the result is obtained within the screening period. Retests should not be completed for UPCR levels unless there is an error found with the test such that the test cannot be completed by the laboratory or an error noted by the site that is conveyed to the sponsor prior to the result being reported.

6. STUDY INTERVENTION

6.1. Study Interventions Administered

Participants in the study will maintain their standard-of-care treatment of MMF/MPA and background glucocorticoid (see also Section 5.1, Inclusion Criterion #5 and Inclusion Criterion #6). The glucocorticoid dose tapering is described in Section 6.5.2 and a tapering schedule is provided in Appendix 7 [Section 10.7].

In addition to remaining on the standard-of-care noted above, participants will be randomized to 1 of 2 treatment groups as described below:

- Guselkumab: Participants will receive guselkumab 400 mg IV at Weeks 0, 4 and 8 (ie, 3 IV doses) and guselkumab 200 mg SC 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 remain on their assigned treatment through Week 48. All participants will receive an IV infusion at Weeks 0, 4, and 8 (either active or placebo) and 2 SC injections (either active or placebo) at Week 12 through Week 48.

Intravenous study intervention (including the flush) should be administered over a period of not less than 1 hour, and not more than 2 hours. The infusion (including the flush) should be completed within 6 hours of preparation.

Since multiple SC injections are administered at visits, each injection of study intervention should be given at a different location of the body.

Study intervention administration must be captured in the source documents and the electronic case report form (eCRF).

Guselkumab and placebo for guselkumab will be manufactured and provided under the responsibility of the sponsor. Refer to the guselkumab IB for a list of excipients. Both guselkumab and placebo are designated as Investigational Medicinal Product.

Detailed instructions on the administration of study intervention will be provided in the Site Investigational Product Procedures Manual and Investigational Product Preparation and Administration Instructions (IPPI).

For a definition of study intervention overdose, refer to Section 8.4, Treatment of Overdose.

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 (Section 1.3).

6.1.1. Long-Term Extension

During the LTE of the study, participants will continue to receive the same study intervention q4w (placebo or guselkumab) that they were assigned to receive through Week 48. The first dose in the LTE will be at Week 52.

The study intervention will remain blinded throughout the study (including the LTE).

Instructions for administration of the study intervention will be provided to participants (or caregiver) who have been trained and would like to administer the study intervention at home.

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 (Section 1.3).

6.1.2. Combination Products

- For this protocol, the term combination product refers to the single integral drug-device combination.
- The sponsor-manufactured combination product for use in the main study is the 1.0 mL prefilled syringe (PFS) (100mg/mL) assembled in an UltraSafe Plus™ Passive Needle Guard (PFS-U). Additional details on the PFS-U are provided in Section 6.2 and the guselkumab IB.
- The sponsor-manufactured combination products provided for use in the LTE (Section 4.1.2) are the 2.0 mL PFS (200mg/2mL) with YpsoMate Autoinjector (PFS-Y) and the 1.0 mL PFS-U (100mg/mL). The YpsoMate device (Y) is manufactured by the medical device manufacturer Ypsomed. The UltraSafe Plus device (U) is manufactured by medical device manufacturer Becton-Dickinson. The sponsor manufactures the 100mg/mL and 200mg/2mL guselkumab PFS. The sponsor also assembles the PFS with the devices to form the PFS-U and PFS-Y combination products. Additional details on the PFS-U and PFS-Y are provided in Section 6.2 and the guselkumab IB.
- All combination product deficiencies (including failure, malfunction, improper or inadequate design, manufacturer error, use error, and inadequate labeling) shall be documented and reported by the investigator throughout the study. For studies using a combination product, these deficiencies will be reported as product quality complaints (PQC) (see Section 10.10.6 Appendix 10: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting) and appropriately managed by the sponsor.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

For IV administration, guselkumab will be supplied as a 100 mg/mL sterile liquid in a single dose PFS assembled in an UltraSafe Plus™ Passive Needle Guard (PFS-U). For IV administration,

placebo for guselkumab will be supplied as a 1 mL sterile liquid in a single dose PFS assembled in a PFS-U. Study intervention will be prepared for IV administration based on the instructions provided to clinical sites in the IPPI.

For SC administration during the main study, guselkumab will be supplied as a 100 mg/mL sterile liquid in a single dose PFS-U. For SC administration, placebo for guselkumab will be supplied as a 1 mL sterile liquid in a single dose PFS-U. For SC administration during the LTE, guselkumab will be supplied as the 2.0 mL PFS-Y (200mg/2mL) or the 1.0 mL PFS-U (100mg/mL). Placebo for guselkumab during the LTE will be supplied as a 1 mL sterile liquid in a single dose PFS-U or 2.0 mL PFS-Y.

Guselkumab and placebo for guselkumab should be clear and colorless to light yellow solution that may contain small translucent particles. Do not use guselkumab or placebo for guselkumab if the liquid is cloudy or discolored or has large particles. Protection from light is not required during the preparation and administration of the study intervention material, but avoid direct exposure to sunlight. Aseptic procedures must be used during the preparation and administration of the study intervention material.

Refer to the site IPPI for additional guidance on study intervention preparation, handling, and storage.

Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. All study intervention will be stored in its original container and disposed of according to the sponsor's instructions.

Study intervention must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study intervention will be documented on the intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the intervention return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for intervention accountability purposes.

Study intervention should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants participating in the study. Returned study intervention must not be dispensed again, even to the same participant. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor.

Further guidance and information for the final disposition of unused study interventions are provided in the Site Investigational Product Procedures Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 intervention groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by geographic region and UPCR level. The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant participant details to uniquely identify the participant.

Blinding

To maintain the study blind, the study intervention container will have a label containing the study name, study intervention number, reference number, and storage conditions. The label will not identify the study intervention in the container. However, if it is necessary for a participant's safety, the study blind may be broken and the identity of the study intervention ascertained. The study intervention number will be entered in the eCRF when the study intervention is administered. The study interventions will be identical in appearance and will be packaged in identical containers.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

Data that may potentially unblind the intervention assignment (ie, study intervention serum concentrations, anti-guselkumab antibodies, study intervention preparation/accountability data, intervention allocation, and biomarker or other specific laboratory data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of DBL and unblinding.

Under normal circumstances, the blind should not be broken until all participants have completed the main study and the database is finalized. The investigator may in an emergency determine the identity of the intervention by contacting the IWRS. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be

informed as soon as possible. The date and reason for the unblinding must be documented in the appropriate section of the eCRF and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

Participants who have had their intervention assignment unblinded should continue to return for scheduled evaluations.

Additionally, a given participant's treatment assignment may be unblinded to the sponsor, the Independent Ethics Committee/Institutional Review Board (IEC/IRB), and site personnel to fulfill regulatory reporting requirements for suspected unexpected serious adverse reactions (SUSARs). If a participant is unblinded by the site, the information must be entered in the appropriate section of the eCRF and in the participant's source documents.

A separate code break procedure will be available for use by J&J Global Medical Safety group to allow for unblinding of individual participants to comply with specific requests from regulatory or health authorities.

In general, randomization codes will be disclosed fully at the end of study when the clinical database is closed.

The study blind will be maintained throughout the study (including the LTE).

One DBL for the study will occur at the end of study.

6.4. Study Intervention Compliance

When study intervention is administered as an IV infusion or SC injection by qualified staff, the details of each administration will be recorded in the eCRF. For IV infusions, this will include date and start and stop times of the IV infusion and volume infused; for SC injections, this will include date and time of SC injection.

Additional details may be provided in the site IPPI that is provided separately. Compliance with the treatment schedule is strongly encouraged.

6.5. Concomitant Therapy

Detailed information of prestudy topical and systemic SLE and LN therapies including dosage and frequency of administration must be recorded for past history as well as any COVID-19 vaccinations and treatments (including authorized for emergency use) at any time in the past. Other prestudy therapies administered at the time of screening or up to 60 days before first dose of study intervention, whichever is longer, must be recorded at screening. For any therapies that were discontinued, the reason for discontinuation (eg, non-response, loss of response, intolerance, safety concern, etc) should be documented.

Concomitant SLE and LN therapies (and non-SLE, LN concomitant therapies) must be recorded throughout the study beginning with screening to the final safety follow-up visit after the last dose of study intervention. Concomitant therapies should also be recorded beyond the final safety

follow-up visit only in conjunction with SAEs that meet the criteria outlined in Serious Adverse Events in Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, or other specific categories of interest) different from the study intervention must be recorded in the eCRF. Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and indication. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a participant into the study.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Every reasonable effort should be made to keep concomitant medications stable to avoid introducing non-protocol medications for SLE or LN disease activity through the final safety visit, or as specified in the following sections. Dose stabilization of all concomitant medications is required prior to randomization. All medications must meet study protocol guidelines (see Sections 5.1 and 5.1.1, and Table 5 and Table 6, which outline permitted concomitant medication use and dose stabilization requirements prior to randomization and during the blinded study period). It is recommended that all other concomitant medications be maintained at stable doses through the final safety visit, including for those discontinuing the study prematurely. If necessary, a concomitant medication may be reduced or temporarily discontinued because of abnormal laboratory values, safety and tolerability issues, concurrent illness, or the performance of a surgical procedure, but the change and reason for the medication change should be clearly documented in the participant's medical record. Adjustments in concomitant therapies that do not comply with the study protocol guidelines may cause a participant to be considered a TF for the primary and secondary endpoints through Week 52.

During the entire study, Investigators should consider whether increases in permitted background therapy due to increased SLE or LN disease activity warrant discontinuation of study intervention. If protocol-prohibited immunosuppressants (such as cyclosporine, voclosporin, or tacrolimus), biologics (such as belimumab or rituximab), cytotoxic agents (such as cyclophosphamide), IV glucocorticoids, or average daily doses of oral glucocorticoids >60 mg (prednisone or equivalent) are initiated for severe, progressive, or unstable SLE disease activity, the participant should be considered for discontinuation from study intervention (see Section 7.1). This should be discussed with the medical monitor and/or sponsor.

During the LTE, every effort should be made to continue to adhere to the requirements for concomitant therapies with some exceptions as specified in the sections below.

Table 5 outlines permitted concomitant medication use and dose stabilization requirements prior to randomization.

In the main study and the LTE, treatment for an LN flare, which is defined as an increase in proteinuria and/or serum creatinine concentration, abnormal urine sediment or a reduction in creatinine clearance rate as a result of active disease requiring a change in an immunomodulatory medication for LN beyond that which is outlined in Table 5 and Table 6 will require discontinuation of study medication.

Table 5: Permitted Concomitant Medications for SLE and LN, the Minimum Stabilization Period before Randomization, and the Maximum Allowed Doses at Study Randomization

Permitted Concomitant Medications for SLE	Stabilization Period Prior to Randomization	Maximum Allowable Dose
Antimalarials (chloroquine, hydroxychloroquine, or quinacrine)	Treated for ≥12 weeks with stable dosing for ≥6 weeks	≤250 mg/day chloroquine (≤3 mg/kg/day) ≤400 mg/day hydroxychloroquine ≤100 mg/day quinacrine
Oral glucocorticoids	Treated for ≥6 weeks with stable dosing ≥2 weeks before randomization. Must not have received epidural, IV, or IM administration of glucocorticoids at a prednisone equivalent dose of >125 mg/day within 6 weeks prior to randomization.	Equivalent to average daily dose of 1 mg/kg/day or ≤60 mg/day of prednisone or its equivalent, whichever is lower
NSAIDs and other analgesics	At least 2 weeks	No more than the usual marketed doses approved in the country where the study is being conducted
Anti-hypertensive medications (ARBs or ACE inhibitors)	At least 2 weeks	No more than the usual marketed doses approved in the country where the study is being conducted.
Non-biologic immunomodulators: MMF MPA	Treated for ≥8 weeks at randomization	 ≤3 g/day ≤2.2 g/day

Abbreviations: ACE=angiotensin-converting enzyme; ARB=angiotensin II receptor blockers; IM=intramuscular; IV=intravenous; LN=lupus nephritis; MMF=mycophenolate mofetil; MPA=mycophenolic acid; NSAID=non-steroidal anti-inflammatory drug; SC=subcutaneous; SLE=systemic lupus erythematosus.

Table 6 summarizes the protocol requirements and any allowed changes in dosing for study-permitted SLE and LN medications during the double-blind study period.

Table 6: Blinded Study Period - Protocol Requirements for Permitted Concomitant SLE or LN Medications

Permitted Concomitant Medications for SLE[a]	Study Dose at Randomization	Maximum Allowable Dose During Study
Antimalarials (chloroquine, hydroxychloroquine, or quinacrine)	≤250 mg/day chloroquine (≤3 mg/kg/day) ≤400 mg/day hydroxychloroquine ≤100 mg/day quinacrine	Stable dosing through Week 52. Initiation of new antimalarial treatment is not permitted through Week 52.
Oral glucocorticoids[b]	Stable oral glucocorticoids at minimum prednisone equivalent dose of 10 mg/day and maximum 1 mg/kg/day or ≤60 mg/day, whichever is lower.	**Week 2 Through Week 12** - tapering starting from Week 2 to prednisone 5 mg equivalent PO daily by Week 12 according to schedule (Appendix 7 [Section 10.7]) Reason(s) for not tapering glucocorticoids should be documented
NSAIDs and other analgesics	Stable dosing through Week 52 with no more than the usual marketed doses approved in the country where the study is being conducted. Notable changes in NSAID dosing to be recorded in concomitant medications. The initiation of treatment with NSAIDs should be avoided unless other analgesics are contraindicated.	
Anti-hypertensive medications (ARBs or ACE inhibitors)	No more than the usual marketed doses approved in the country where the study is being conducted. The initiation of treatment with ARB or ACE inhibitors should be avoided between randomization and Week 52 unless other hypertensive treatments are contraindicated. Substitution of ACE inhibitors for ARBs or ARBs for ACE inhibitors is permitted if medically necessary.	
Non-biologic immunomodulators: MMF MPA	 ≤3 g/day ≤2.2 g/day	Stable dosing through Week 52. Initiation of a new immunomodulator is not permitted through Week 52.

[a] Permitted concomitant medications are not supplied by the sponsor.

[b] Between Weeks 12 and 52, participants requiring average daily doses of glucocorticoids for SLE or LN disease activity that exceed their baseline dose at Week 0 may be categorized as TFs. While these participants will be permitted to remain in the study, the investigator must consider whether glucocorticoid dose increases to an average daily dose ≥60 mg prednisone or equivalent for more than 7 consecutive days or whether a requirement for multiple rescues with glucocorticoid therapy between Weeks 12 and 52 should result in discontinuation of study intervention administration (see Section 7.1).

Abbreviations: ACE=angiotensin-converting enzyme; ARB=angiotensin II receptor blockers; IM=intramuscular; IV=intravenous; LN=lupus nephritis; MMF=mycophenolate mofetil; MPA=mycophenolic acid; NSAID=non-steroidal anti-inflammatory drug; PO=orally; SC=subcutaneous; SLE=systemic lupus erythematosus.

6.5.1. Antimalarial Medications

Stable treatment with hydroxychloroquine, chloroquine, or quinacrine is permitted through Week 52 as shown in Table 5 and Table 6. It is not permitted to introduce or adjust dosing of antimalarials through Week 52; however, if necessary, one antimalarial may be substituted for another at an equivalent or lower dose. Antimalarials produced by a licensed compounding pharmacy (eg, quinacrine) in the country of administration and using pharmaceutical grade components are allowed. It is recommended that participants receiving antimalarials receive screening for retinal toxicity according to local guidelines.

During the LTE, antimalarial doses or medications may be changed in order to treat other aspects of SLE as needed, but should not be changed to treat LN.

6.5.2. Glucocorticoid Therapy

Participants likely to require multiple courses of systemic glucocorticoids for reasons other than SLE or LN (eg, history of uncontrolled asthma, uncontrolled chronic obstructive pulmonary disease, etc) should be excluded from study participation, including the LTE. However, participants may receive short courses (10 days or less) of oral glucocorticoids for reasons such as prophylactic therapy before surgery (stress-dose glucocorticoids), therapy for certain infections, acute exacerbation of asthma or chronic obstructive pulmonary disease, or other condition (eg, contact dermatitis) not related to increased SLE or LN disease activity. Dosage, duration, and reason for glucocorticoid use in these instances must be documented.

Unnecessary changes in glucocorticoid dose are discouraged, and any dose adjustments are recommended to be made in small amounts. Changes in glucocorticoid dosing other than those described in this section of the protocol are allowed only for medical necessity. The degree and timing of any unspecified glucocorticoid adjustments should be carefully considered as this may have a significant impact on the study results and upon continuation of study intervention.

Oral Glucocorticoids

Participants must be receiving this medication at screening and be on a stable dose equivalent to an average daily dose of 1 mg/kg/day or ≤60 mg/day prednisone (or equivalent), whichever is lower for at least 2 weeks prior to the first study intervention dose. Participants are required to be receiving at least 10 mg/day prednisone equivalent at screening and randomization.

A summary of allowed glucocorticoid dosing at randomization and changes during the study are shown in Table 5 and in Table 6, respectively. A glucocorticoid tapering schedule starting from Week 2 down to 5 mg po qd prednisone equivalent by Week 12 is provided in Appendix 7 [Section 10.7]. It is required that all participants adhere to this steroid tapering schedule as closely as possible. Significant deviation from this tapering schedule should be discussed with the medical monitor. Glucocorticoid doses should not be changed to start within one of the columns of the tapering schedule. If a participant falls between the doses noted in 2 adjacent columns (eg, 55 mg instead of 50 or 60 mg), the investigator should make a clinical decision as to which column they should be tapered to (eg, 30 or 40 mg) then stay within that column for the rest of the taper. A participant's lowest glucocorticoid dose should be 5 mg po qd through Week 24 unless an AE requires discontinuation. Reason(s) for not tapering glucocorticoids should be documented.

Additional considerations of oral glucocorticoid use during the study are as follows:

- If a participant experiences worsening disease activity while tapering glucocorticoids from Weeks 2 to 12, further dose decreases may be suspended, and/or their oral glucocorticoid dose may be temporarily increased (ie, glucocorticoid rescue) if deemed necessary by the investigator.

- Increases in average daily glucocorticoid dose that exceed the baseline dose may trigger TF rules. If glucocorticoid tapering is interrupted, Investigators are encouraged to resume tapering as soon as it is practical.
- Increases above 10 mg/day prednisone equivalent after Week 12 will be considered a TF.
- It is recommended that participants be educated about and monitored for symptoms of steroid adrenal insufficiency/deficiency (eg, Addisonian symptoms such as fatigue, muscle weakness, decreased appetite, nausea, vomiting, joint and muscle pain) by study staff during periods of steroid tapering, as appropriate.
- After Week 24, further tapering of glucocorticoids is permitted, however, the taper should not exceed a decrease of 1 mg/day prednisone equivalent per month (eg, 5 mg/day to 4 mg/day over a 1-month time period). Investigators should monitor these participants for signs and symptoms of Addisonian crisis.

Epidural, Intravenous, Intramuscular, Intra-articular, Intrabursal injection, and Intralesional Glucocorticoids

Epidural, IV, and IM glucocorticoids at a prednisone equivalent dose of >125 mg/day should not be used during the study or within 6 weeks prior to randomization.

Intra-articular (IA), intrabursal, or intralesional administration of glucocorticoids is strongly discouraged within 6 weeks prior to randomization. Use of an intrabursal or intralesional glucocorticoid is highly discouraged but is allowed if no other treatments are available.

ACTH administered by injection is not allowed within 1 month prior to randomization and throughout the study.

During the study, use of epidural, IV, IM glucocorticoid use may cause participants to be considered TFs. If use of epidural, IV or IM glucocorticoids is planned for a participant, discussion with the medical monitor is recommended.

If clinically necessary, a total of up to 2 IA injections may be permitted for SLE up to Week 12 and should be recorded as a medical procedure.

Rectal Administration

Rectal administration of glucocorticoids, if necessary, should be short-term and topical preparations should be used.

Inhalation Glucocorticoids

Glucocorticoids administered by bronchial or nasal inhalation for treatment of conditions other than SLE or LN may be given as needed.

6.5.3. Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) and other regularly administered analgesics should not be adjusted for at least 2 weeks prior to the first administration of the study intervention and through Week 52, and they may be changed only if the participant develops unacceptable side

effects. Participants are permitted to receive the usual marketed doses approved in the country in which the study is being conducted. NSAIDs, including aspirin or selective cyclooxygenase-2 inhibitors, and other analgesics (including injectable NSAIDs, analgesics or other pain-relieving agents) that are used on an "as needed" basis would generally not be considered to constitute stable dosing as noted is required in Table 5 and Table 6. The initiation of treatment with NSAIDs should be avoided unless other analgesics are contraindicated. Participants using them in specific situations (eg, prior to an activity) may be considered stable but these situations should be discussed with the medical monitor or sponsor prior to enrollment into the study.

6.5.4. Anti-hypertensive Medications

Participants are permitted to receive stable doses of ARB or ACE inhibitors for the treatment of hypertension, cardiovascular disease, kidney disease, and LN. If receiving regular treatment with ACE inhibitors or ARBs, participants must be receiving stable dosing for at least 2 weeks prior to randomization. If necessary, participants are permitted to switch between ARB and ACE inhibitors or vice versa. Effort should be made to ensure that the effective doses of the switched drugs are comparable. The initiation of treatment with ARB or ACE inhibitors should be avoided between randomization and Week 52 unless other hypertensive treatments are contraindicated.

During the LTE, the dose of ACE inhibitors/ARBs may be changed or ACE inhibitors/ARBs may be initiated, if needed to help with blood pressure control or because of specific medication availability and/or convenience (eg, using combined ARB hydrochlorothiazide medications), but medication changes to treat LN flares would require discontinuation from the LTE.

6.5.5. Non-biologic Immunomodulators

Stable dosing of MMF or MPA as described in Table 5 is required. No other immunomodulators are permitted during the study. A reduction in immunomodulators is allowed only if the participant develops unacceptable side effects, with the implication that this may affect interpretation of the participant's clinical data. There should be no additions of a new immunomodulator to the existing treatment regimen.

For subjects who initiate MMF (or MPA) during screening or close to screening, the dose should be titrated up during screening based on tolerability to a target dose of ≤3.0 grams/day MMF (or equivalent MPA) and kept stable thereafter.

6.5.6. Topical Medications

Regular use of topical medications is permitted. "As needed" use of topical NSAIDs, analgesics, or other pain-relieving agents such as capsaicin is permitted, but not within 48 hours prior to study visit. "As needed" use of topical glucocorticoids is permitted if involving a limited BSA (≤20%), but not within 48 hours prior to a study visit.

6.5.7. Prohibited Therapies

Use of additional immunosuppressants or immunomodulators, other than those explicitly allowed in the inclusion/exclusion criteria (Section 5.1 and 5.1.1), are prohibited including, but not limited to, the following:

- Agents targeted at reducing TNFα (eg, infliximab, golimumab, certolizumab pegol, etanercept, CT-P13, adalimumab)
- B-cell targeted agents (anti-CD20 [eg, rituximab, obinutuzumab], anti-CD19 [eg, obexelimab (XmAb5871)], anti-B-cell activating factor, also known as B lymphocyte stimulator [BLyS; eg, belimumab], anti-CD22 [eg, inotuzumab, ozogamacin], or other B-cell targeted therapies, such as tabalumab, atacicept, daratumumab)
- IL-1 inhibitors (eg, canakinumab)
- IL-2 inhibitors or exogenous IL-2 therapy
- IFN inhibitors or exogenous IFN therapy
- IL-1 receptor antagonists (eg, anakinra)
- Tocilizumab or any other biologic targeting IL-6 or IL-6 receptor
- Tofacitinib, baricitinib, upadacitinib, or any other janus kinase inhibitor
- Abatacept
- Anti-IL-17 agents (eg, brodalumab, secukinumab, or ixekizumab)
- Leflunomide
- Cyclosporine A except for topical use
- Calcineurin inhibitors (eg, tacrolimus or pimecrolimus, voclosporin)
- Sirolimus, everolimus
- Immunomodulatory preparations (eg, MTX, AZA/6-MP, mizoribine)
- Toll-like receptor inhibitors
- Thalidomide or lenalidomide
- Dapsone
- ACTH by injection
- Epidural, IV, and IM glucocorticoids (see Section 6.5.2)
- Other investigational agents

Use of cytotoxic drugs is prohibited including, but not limited to, cyclophosphamide, chlorambucil, nitrogen mustard, or other alkylating agents.

Multiple administrations of high doses of oral glucocorticoids (average daily dose ≥60 mg), or initiation of high potency topical glucocorticoids (>20% BSA), are prohibited during the study as defined in Section 6.5.2.

Sulfa-based antibiotics, where reasonable and necessary, are allowed but should generally be avoided.

The use of complementary therapies (eg, herbs, ointments, traditional Chinese medicine, acupuncture) that have the potential to activate or inhibit the immune system is prohibited (see

Section 5.1.1). In addition, use of complementary therapies that have the potential to interact with antithrombotic agents is prohibited in those taking antithrombotic agents.

The use of other complementary therapies is strongly discouraged; in individual cases, use may be permitted following discussion with the study sponsor and/or medical monitor.

As these lists cannot be exhaustive, please consult the medical monitor to discuss prior to starting any biologic or other advanced therapies.

6.5.8. Rescue Medication

Higher doses of steroids can be used as rescue medication, however this may trigger a TF (see Section 6.5.2 for details on glucocorticoid therapy concomitant use).

Increases in doses of current medications or addition of new protocol permitted medications for SLE or LN disease activity, such as NSAIDs, ACE inhibitors, ARBs, immunomodulators (antimalarials) and, potentially, topically applied (>20% BSA) or locally injected therapies (if clinically indicated) should be discussed with the medical monitor and/or sponsor.

Severe, progressive, or unstable worsening of SLE disease activity that requires escalation in therapy, including biologics such as belimumab or rituximab, systemic immunomodulators such as cyclosporine or tacrolimus, sustained high doses of oral glucocorticoids, use of IV glucocorticoids, or use of cytotoxic agents such as cyclophosphamide may require discontinuation from the study intervention (see Section 6.5 and Section 7.1).

6.5.9. Vaccinations (including COVID-19)

When considering use of locally approved vaccines (including emergency use authorized COVID-19 vaccines) in study participants, follow applicable local vaccine labelling, guidelines, and standards of care for patients receiving immune-targeted therapy.

For study participants receiving a locally-approved COVID-19 vaccine (including emergency use authorized), in order to help identify acute reactions potentially related to COVID-19 vaccine, it is recommended where possible that vaccine and study drug be administered on different days, separated by as large an interval as is practical within the protocol.

6.6. Dose Modification

Not applicable.

6.7. Continued Access to Study Intervention After the End of the Study

Local regulations on continued access will always take precedence. Plans for continued access stated in this protocol may change if new information on the benefit-risk profile of guselkumab becomes available during the study or program.

At the end of their participation in the main study, participants who have completed the study and are benefiting from the study intervention, as determined by meeting CRR at Weeks 48 and 52, will be offered the opportunity to enter the LTE study.

If a DMC review performed prior to the first patient's entry into the LTE or during the LTE demonstrates unfavorable benefit:risk profile or safety concerns arise, the study (and LTE) may be stopped.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

- The participant withdraws consent to receive study intervention.
- The investigator believes that for safety reasons or tolerability reasons (eg, AEs) it is in the best interest of the participant to discontinue study intervention.
- The participant becomes pregnant within the study period. Refer to Appendix 5 [Section 10.5], Contraceptive Guidance and Collection of Pregnancy Information.
- The participant develops an opportunistic infection (this does not include candidiasis that is limited to the mouth).
- The participant is deemed ineligible according to the following TB screening criteria:

  A diagnosis of active TB is made.

  A participant has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination, or has had recent close contact with a person with active TB, and cannot or will not continue to undergo additional evaluation.

  A participant undergoing evaluation has a chest radiograph with evidence of current active TB and/or a positive QuantiFERON-TB® test result (and/or a positive tuberculin skin test result in countries in which the QuantiFERON-TB® test is not approved/registered or the tuberculin skin test is mandated by local health authorities), unless active TB can be ruled out and appropriate treatment for latent TB can be initiated prior to the next study intervention administration and continued to completion (see also Section 8.2.11 and Appendix 3 [Section 10.3]). Indeterminate QuantiFERON-TB® test results should be handled as described in Section 8.2.11. Participants with persistently indeterminate QuantiFERON-TB® test results may continue without treatment for latent TB if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the participant has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the medical monitor or designee and recorded in the participant's source documents and initialed by the investigator.

  Note: In Ukraine, while the QuantiFERON-TB® test is not approved/registered, it is acceptable, and an additional tuberculin skin test is not required.

  A participant receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.

- The participant has a serious adverse reaction that is related to an injection or an infusion resulting in bronchospasm with wheezing and/or dyspnea that requires ventilatory support OR that results in symptomatic hypotension with a decrease in systolic blood pressure >40 mm Hg or blood pressure <90/60 mm Hg.
- The participant has a reaction resulting in myalgia and/or arthralgia with fever and/or rash (suggestive of serum sickness and not representative of signs and symptoms of other recognized clinical syndromes) occurring 1 to 14 days after an injection of study intervention. These may be accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache.
- The participant has a malignancy including squamous cell skin cancer. Consideration may be given to allowing participants who develop ≤2 basal cell skin cancers that are adequately treated with no evidence of residual disease to continue to receive study intervention.
- Participant requires dialysis.
- Noncompliance with study drug administration defined as multiple episodes of missing the window in which to receive study intervention.
- The participant has severe liver test abnormalities that meet one of the conditions outlined in Appendix 11 (Section 10.11; Liver Safety: Suggested Actions and Follow-up Assessments).

The sponsor may elect to terminate the study at any time, and if the sponsor decides not to continue development for any reason, study medication/drug will no longer be provided to any participants, including those in the LTE.

Discontinuation of a participant's study intervention should be considered under the following conditions:

1. Persistent inadequate response or worsening of LN based on worsening of renal function.
2. If the participant initiates treatment with prohibited therapies for SLE or LN, the medical monitor or designee should be notified for possible discontinuation of study intervention (Section 6.5).
3. The participant develops a serious infection, including but not limited to sepsis or pneumonia.

   Note: Any serious infection should be discussed with the medical monitor or designee, and study intervention should be withheld until the clinical assessment is complete.

4. Discontinuation of study treatment should be considered for participants who report suicidal Ideation level 4 (some intent to act, no plan), Ideation level 5 (specific plan and intent), or any suicidal behavior (actual suicide attempts, interrupted attempts, aborted attempts, or preparatory actions) on a postbaseline (after Week 0) eC-SSRS assessment. Discussion of such subjects with the medical monitor or designee is required.
5. The participant develops a severe injection-site or infusion reaction, but not meeting criteria specified above.

If a participant discontinues study intervention for any reason before the end of the double-blind phase they may continue in the study. If the participant wishes to discontinue the study, then the Final Efficacy Visit and final safety visit assessments should be obtained as specified in the SoA

(Section 1.3, or as noted in Footnote c of the SoA). Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant.

7.1.1. Long-Term Extension

Participants may withdraw consent and discontinue treatment during the LTE at any time. A participant's treatment must be discontinued in the LTE if any of the criteria in Section 7.1 above are met. In addition, study intervention will be discontinued if the participant has an LN flare that requires a change in medication during the LTE.

If a participant permanently discontinues study intervention for any reason before the end of the LTE, assessments should be obtained as specified in SoA (Table 2 and Table 3).

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death
- Sponsor decision (eg, participating in any other clinical study with an investigational agent)

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. Participants who terminate study participation will not be required to return for any follow-up assessments; however, these participants should complete the safety and efficacy evaluations specified in the SoA (Section 1.3) at the time they terminate study participation. If the reason for withdrawal from the study is withdrawal of consent then no additional assessments are allowed.

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply as local regulations permit.

Prior to a participant withdrawing consent for follow-up, the investigator should offer the participant an opportunity for one of the alternative reduced follow-up mechanisms described below. Participants will not be allowed to continue to receive study intervention if reduced follow-up is in place, but other study evaluations should continue as much as possible. Withdrawal of consent should be an infrequent occurrence in clinical studies[30], therefore, prior to the start of the study the sponsor and the investigator should discuss and reach a clear understanding of what constitutes withdrawal of consent in the context of the available reduced follow-up mechanisms listed.

Circumstances for Reduced Follow-up

In the situation where a participant may be at risk for withdrawal of consent and is unable to return for scheduled visits at the protocol-defined frequency, the investigator may consider options for

reduced follow-up with consultation of the sponsor and/or medical monitor. These may include (as local regulations permit):

- Less frequent clinical visits
- Telephone, email, letter, social media, fax, or other contact with:
  - participant
  - relatives of the participant
  - participant's physicians (general or specialist)
- Review of any available medical records

Details regarding these contacts must be properly documented in source records including responses by participants.

7.2.1. Withdrawal From the Use of Research Samples

A participant who withdraws from the study will have the following options regarding the optional research samples:

- The collected samples will be retained and used in accordance with the participant's original separate informed consent for optional research samples.
- The participant may withdraw consent for optional research samples, in which case the samples will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

Withdrawal From the Optional Research Samples While Remaining in the Main Study

The participant may withdraw consent for optional research samples while remaining in the study. In such a case, the optional research samples will be destroyed. The sample destruction process will proceed as described above.

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Appendix 9 [Section 10.9], Regulatory, Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF and in the separate ICF for optional research samples.

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to randomization attempts should be made to obtain contact information from each participant, eg, home, work, and

mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study-site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods). These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The SoA summarizes the frequency and timing of efficacy, PK, immunogenicity, PD, biomarker, pharmacogenomic, and safety measurements applicable to this study.

All patient-reported outcome (PROs) assessments should be completed before any tests, procedures, or other consultations to prevent influencing participant perceptions. All PROs should be completed independently by study participants. It is recommended that PROs be completed in the following sequence: FACIT-Fatigue, PGIC, lupus symptoms (assessment of joint pain, joint stiffness, rash, swelling), and LupusQoL. Clinician-reported outcome (ClinRo) procedures to be performed include: SLEDAI-2K, Physician's Global Assessment (PGA), joint count assessment, CLASI. Clinician-reported outcome assessments should be performed by an adequately trained assessor (see Section 8.1 for details).

Additional urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

Spot urine will be used for UPCR related analyses (including the primary endpoint and various other key efficacy endpoints). Analysis of the primary endpoint based on UPCR is discussed in Section 9.4.2. Refer to the SoA (Section 1.3) for the timing and frequency of these sample collections. Instructions on the sample collection and handling of urine samples are described in the laboratory manual.

Screening Phase

The screening phase is up to 8 weeks duration before randomization (with up to 4 additional weeks for those starting MMF/MPA at or near the beginning of screening). After written informed consent has been obtained, all screening evaluations (eg, laboratory test results, clinical data, and concomitant medication data) that establish participant eligibility will be performed by the principal investigator or designee to confirm that the participant satisfies all inclusion criteria and does not violate any exclusion criteria. Participants who meet all of the inclusion and none of the exclusion criteria can be enrolled in the study. **Participants must meet criteria for UPCR, hematology, and chemistry after at least 8 weeks of MMF/MPA**. Every effort should be made to adhere to the SoA (Section 1.3) for each participant. The collection of AEs will start at the time informed consent is obtained.

Participants must undergo testing for TB and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB (Section 8.2.11 and Appendix 3 [Section 10.3]).

Women of childbearing potential must have a negative urine pregnancy test result at screening and at each visit and before any study intervention administration. Participants who are women of childbearing potential must be reminded that they are required to use a highly effective method of contraception during the study (as described in Section 5.1, Inclusion Criterion 17 and Appendix 5 [Section 10.5]) and must continue taking such precautions for 12 weeks after receiving the last dose of study intervention. The method(s) of contraception used by each participant must be documented.

All screening evaluations establishing participant eligibility will be performed and reviewed by the investigator before a participant can be randomized. Participants must have received approval for study randomization following adjudication of inclusion and exclusion criteria.

A kidney biopsy is required if one has not been done within the last 6 months prior to screening to confirm Class III/IV (ISN/RPS) proliferative nephritis (with or without class V [ISN/RPS] membranous nephritis). A de-identified copy of the pathology report will be required to be provided, tissue samples will be requested (where applicable or where local regulations permit) for all kidney biopsies during screening or within the last 6 months. If the participant is undergoing a kidney biopsy during screening, the participant should meet all other eligibility criteria prior to a biopsy being performed.

Documentation (historical or local laboratory testing) of unequivocally positive values (as defined in the laboratory's reference range) should be provided for the following: ANA (eg, ANA by human epithelial type 2 cells [HEp-2] titer, ANA by enzyme-linked immunosorbent assay [ELISA]), or anti-dsDNA (eg, anti-dsDNA by Farr assay or ELISA), or anti-Smith. To establish participant eligibility, these results must be confirmed through central laboratory testing.

Blood Sample Collection

During the main study, the total blood volume to be collected from each participant will be approximately 720 mL for those at sites collecting biomarkers, and approximately 380 mL for

those at sites not collecting biomarkers. During the LTE, the total blood volume to be collected from each participant will be approximately 270 mL for those at sites collecting biomarkers, and approximately 215 mL for those at sites not collecting biomarkers.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form.

Refer to the SoA (Section 1.3) for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Investigator Site File (includes protocol and IB)
- IPPI
- Laboratory Manual
- eCRF completion instructions
- Patient recruitment materials
- Sample ICFs
- IWRS Manual
- ePRO equipment
- Laboratory kits
- Pharmacy manual/study site investigational product and procedures manual
- PRO questionnaires
- Participant Diary Card (LTE only)

8.1. Efficacy Assessments

Investigator assessments and PROs of efficacy are included in this section.

- The PRO instrument will be provided in the local language in accordance with local guidelines.
- The PRO instrument must be available for regulators and for IRB/IEC submissions.

- The PRO and adverse event data will not be reconciled with one another.

8.1.1. SLE Disease Activity Index 2000

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.[35,36] 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.

8.1.2. Physician's Global Assessment of Disease Activity

The PGA[27,28] independent of participants' assessment is recorded on a 10-cm VAS with responses ranging from 0-3, and verbal anchors "No disease activity" (0) on the far-left side of the scale and "Severe disease activity" (3) on the far right of the scale. Disease activity can range from 0 representing no disease activity, 1 representing mild disease activity, 2 representing moderate disease activity, to 3 representing extremely active disease. The baseline measurement for the PGA is defined as the closest measurement taken prior to the initiation of the Week 0 administration.

No worsening in PGA defined as no significant deterioration (<10% increase from baseline) using a 10-cm visual analogue scale.[10]

8.1.3. Joint Count Assessments

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 (Section 1.3). 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. The joint assessor should preferably be a rheumatologist, but if a rheumatologist is not available, it should be a health care provider with at least 1 year of experience in performing joint assessments. A health care provider with less than 1 year of experience may serve as a joint assessor based upon the approval of the sponsor. 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.

8.1.4. Cutaneous Lupus Erythematosus Disease Area and Severity Index

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 CLE patients with or without systemic involvement.[1] 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 nonscarring 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.[1]

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

8.1.5. 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.[7,17]

8.1.6. Patient Global Impression of Change

The Patient Global Impression of Change (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.[10]

The PGIC uses a 7-point Likert Scale on which patients rate the change in their LN since baseline by choosing one of the following response options: "Very much improved" (1); "Much improved" (2); "Minimally improved" (3); "No change" (4); "Minimally worse" (5); "Much worse"(6); "Very much worse" (7).

The PGIC will also serve as an anchor measure to explore clinically meaningful change thresholds for the other patient-reported outcomes included in the study.

8.1.7. Lupus Symptoms

Participants will be asked to report the 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 (Section 1.3).

8.1.8. Lupus Quality of Life Questionnaire

The LupusQoL Questionnaire is a valid, lupus-specific assessment of HRQoL consisting of 34 items across 8 domains (Physical health, Emotional health, Body image, Pain, Planning, Fatigue, Intimate relationships, and Burden to others) developed 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.[21]

8.2. Safety Assessments

Details regarding the external, independent DMC are provided in Section 9.5.

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting, and Appendix 10 [Section 10.10], Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the timepoints provided in the SoA (Section 1.3).

Study participants who are trained to self-inject (or will have a trained caregiver to inject) study intervention at home will be trained to perform self-evaluation for injection-site reactions and reporting of AEs after administering study interventions at home. Study participants will be asked to self-identify signs or symptoms related to certain events (eg, potential TB infection, pregnancy, malignancy) before administering study interventions and will be asked to contact the study site doctor before administration if a symptom is identified.

8.2.1. Physical Examinations

For screening and the final safety visit, a full physical examination will be performed including: the head and neck, chest, abdomen, and extremities, as well as including examinations based on the individual's medical history and manifestations of SLE and LN (edema, skin manifestations, arthritis, etc.).

Assessment of the participants for safety and efficacy requires some physical examination by an investigator at all visits. Targeted physical examinations, height and weight, and evaluation of signs and symptoms of infection, will be performed as specified in the SoA (Section 1.3). Participants will be instructed to remove shoes and outdoor apparel and gear prior to measurements for height and weight.

8.2.2. Vital Signs

Through Week 52, temperature, pulse/heart rate, respiratory rate, and blood pressure will be assessed at each visit. Blood pressure and pulse/heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. If feasible, blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

Through Week 52, at a study intervention administration visit, vital signs should be obtained before, approximately every 30 minutes during, and twice (at approximately 30-minute intervals) after completion of the IV infusion(s), or before and approximately 30 minutes after the SC injection, or if the participant reports any symptoms.

After Week 52 (during the LTE), vital signs will only be assessed when study participants receive study intervention administration at the study site and at the final safety visit. Vital signs will be assessed at these visits as described above in the SoA.

8.2.3. Electrocardiograms

A 12-lead electrocardiogram (ECG) will be performed at screening.

During the collection of the ECG, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same timepoint as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology and urine samples for urinalysis will be collected as noted in Section 1.3. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

The following tests will be performed by the central laboratory unless otherwise specified or approved by the medical monitor or designee:

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

  A medical monitor or designee and the clinical site will be notified if pre-specified abnormal laboratory values defined in the laboratory manual are identified in any participant during the conduct of the study.

- Viral serology (HIV antibody, hepatitis B surface antigen [HBsAg], anti-HBs, Hepatitis B core antibody total, and HCV antibody)
- QuantiFERON® -TB test
- TB skin test (where applicable; performed locally)
- Urine Analyses- Fresh spot urine

  Urinalysis using urine dipstick. Urine sample will be further analyzed.

  Urinary protein/creatinine ratio will be analyzed using an aliquot of spot urine collected from participants.

  Urine sediment microscopy (assessment using spot urine samples), with features analyzed to include (SoA: Section 1.3):

  - Red blood cells
  - WBC
  - Epithelial cells
  - Crystals
  - Red blood cells, WBC, or heme-granular casts
  - Bacteria
- Urine pregnancy testing for women of childbearing potential only (performed locally)

Dipstick and sediment analysis of the urine samples will be performed. Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, and urobilinogen will be determined using a dipstick.

8.2.5. Electronic Columbia-Suicide Severity Rating Scale

No signal of suicidal ideation and behavior has been observed in the clinical trials of guselkumab to date. However, in light of reports concerning suicidal ideation and behavior in patients with plaque psoriasis treated with an IL-17R antagonist (brodalumab),[6] the 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, subject self-report eC-SSRS questionnaire, including standardized questions, follow-up prompts, error handling routines, and scoring conventions.[24,29] 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.

Participants will complete the eC-SSRS questionnaire using the sponsor-provided electronic device. Study site personnel will train the participants on how to use the electronic device. The eC-SSRS will be provided in the local languages in accordance with local guidelines.

The eC-SSRS will be performed during each evaluation visit according to the SoA. During a visit, participants will be directed to a private, quiet place with the electronic device to complete the assessment. Participants who do not have suicidal behavior or ideation will answer a limited

number of questions and will usually complete the assessment in about 3 minutes. Participants with significant suicidal ideation and behavior may require up to 10 minutes to answer all relevant questions. At the screening visit, the eC-SSRS should be completed as the first assessment after signing informed consent and before any other tests, procedures, or other consultations. For subsequent visits, the eC-SSRS should be completed after all PROs and before any other tests, procedures, or other consultations.

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).

Positive reports are generated from the eC-SSRS vendor for ANY of the following findings:

- Ideation level 4: Some intent to act, no plan
- Ideation level 5: Specific plan and intent
- Behaviors: Actual suicide attempts
- Behaviors: Interrupted attempts
- Behaviors: Aborted attempts
- Behaviors: Preparatory actions.

Negative suicidality indication reports are generated from the eC-SSRS vendor when there are NO indications of the above.

The participant should not leave the site at screening or be dosed at dosing visits before the eC-SSRS Findings Report (both for negative and positive reports) is reviewed by the investigator and the participant's risk has been assessed and follow-up determined, as appropriate.

For each Ideation level and Behavior, the following actions and associated alerts will be generated, if applicable:

- No ideation with No Behaviors: No further action is needed.
- Ideation Levels (1-5) or suicidal behavior: Participant risk assessed and referral to a mental health professional.

    Ideation level of a 1, 2, or 3 with No Behaviors: Negative findings report will be generated.

Ideation level of a 4 or 5 or any suicidal behavior: Positive findings report will be generated. When the system reports that the participant has a positive suicidal indication (including for an incomplete-positive assessment), the site can immediately see the outcome via the electronic device.

- Non-suicidal, self-injurious behavior YES: Participant risk assessed and referral to a mental health professional. Negative findings report will be generated.

Interruption or the discontinuation of study treatment should be considered for any participant who reports suicidal Ideation level 4 (some intent to act, no plan), Ideation level 5 (specific plan and intent), or any suicidal behavior (actual suicide attempts, interrupted attempts, aborted attempts, or preparatory actions) on a postbaseline (after Week 0) eC-SSRS assessment and who is deemed to be at risk by the investigator based upon evaluation by a mental health professional. Discussion of such participants with the medical monitor or designee is required (see Section 7.1). The final decision on suitability for continuing in the study will be made by the investigator.

Any eC-SSRS findings, which in the opinion of the investigator are new or considered to be a worsening and clinically significant, should be reported on the AE eCRF (see Appendix 10 [Section 10.10], Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

8.2.6. Concomitant Medication Review

Concomitant medications will be reviewed at each visit.

8.2.7. Injection-Site Reactions

An injection-site reaction is any adverse reaction at a SC study intervention injection-site. Injection sites will be evaluated for reactions and any injection-site reaction will be recorded as an AE.

8.2.8. Hypersensitivity Reactions

Before any administration of study intervention at the study site, appropriately trained personnel and medications (eg, antihistamines, injectable epinephrine) must be available to treat hypersensitivity reactions, including anaphylaxis. All participants must be observed carefully for signs and symptoms of a hypersensitivity reaction (eg, urticaria, pruritis, angioedema, wheezing, dyspnea, or hypotension).

8.2.9. Adverse Events Temporally Associated with Infusion

Any AE (except laboratory abnormalities) that occurs during or within 1 hour after the IV infusion of study intervention will be carefully evaluated. Minor infusion-related AEs may be managed by slowing the rate of the IV infusion and/or treating with antihistamines and/or acetaminophen (paracetamol) as clinically indicated. If an IV infusion of study intervention is interrupted because of an AE that, in the opinion of the investigator, is not severe or does not result in an SAE, the infusion may be restarted with caution.

8.2.10. Infections

Investigators are required to evaluate participants for any signs or symptoms of infection at scheduled visits. Study intervention administration should not be given to a participant with a clinically significant, active infection. If a participant develops a serious infection, including but not limited to sepsis or pneumonia, discontinuation of study intervention must be strongly considered (Section 7.1). Any serious infection should be discussed with the medical monitor or designee, and study intervention should be withheld until the clinical assessment is complete.

8.2.11. Tuberculosis Evaluations

8.2.11.1. Initial Tuberculosis Evaluation

Participants must undergo testing for TB (refer to Appendix 3 [Section 10.3]) and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. The participant should be asked about past testing for TB, including chest radiograph results and responses to tuberculin skin or other TB testing. Investigators have the option to use both the QuantiFERON-TB® test and the tuberculin skin test to screen for latent TB if they believe, based on their judgment, that the use of both tests is clinically indicated to evaluate a participant who is high risk of having latent TB. If either the QuantiFERON-TB® test or the tuberculin skin test is positive, the participant is considered to have latent TB infection for the purposes of eligibility for this study.

Participants with a negative QuantiFERON-TB® test result (and a negative tuberculin skin test result in countries in which the QuantiFERON-TB® test is not approved/registered or the tuberculin skin is mandated by local health authorities) are eligible to continue with pre-randomization procedures. Participants with a newly identified positive QuantiFERON-TB® test result must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB. Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised patients. If no local country guidelines for immunocompromised patients exist, US guidelines should be followed, or the participant will be excluded from the study.

A participant whose first QuantiFERON-TB® test result is indeterminate should have the test repeated. In the event that the second QuantiFERON-TB® test result is also indeterminate, the participant may be enrolled without treatment for latent TB if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the participant has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the medical monitor or designee and recorded in the participant's source documents and initialed by the investigator.

8.2.11.2. Ongoing Tuberculosis Evaluation

Early Detection of Active Tuberculosis

To aid in the early detection of TB reactivation or new TB infection during study participation, participants must be evaluated for signs and symptoms of active TB at scheduled visits (refer to the SoA in Section 1.3) or by telephone contact approximately every 8 to 12 weeks. The following series of questions is suggested for use during the evaluation:

- "Have you had a new cough of >14 days' duration or a change in a chronic cough?"
- "Have you had any of the following symptoms:

  Persistent fever?

  Unintentional weight loss?

  Night sweats?"
- "Have you had close contact with an individual with active TB?" (If there is uncertainty as to whether a contact should be considered "close," a physician specializing in TB should be consulted.)

If the evaluation raises suspicion that a participant may have TB reactivation or new TB infection, an immediate and thorough investigation should be undertaken, including, where possible, consultation with a physician specializing in TB.

Investigators should be aware that TB reactivation in immunocompromised participants may present as disseminated disease or with extrapulmonary features. Participants with evidence of active TB should be referred for appropriate treatment.

Participants who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph, a repeat QuantiFERON®-TB test, a repeat tuberculin skin test in countries in which the QuantiFERON®-TB test is not approved/registered or the tuberculin skin test is mandated by local health authorities, and, if possible, referral to a physician specializing in TB to determine the participant's risk of developing active TB and whether treatment is warranted. Study intervention administration should be interrupted during the investigation. A positive QuantiFERON®-TB test or tuberculin skin test result should be considered detection of latent TB. Participants with a newly identified positive QuantiFERON-TB® test result must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB. Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised patients. If no local country guidelines for immunocompromised patients exist, US guidelines should be followed, or the participant will be excluded from the study. If the QuantiFERON-TB® test result is indeterminate, the test should be repeated. Participants should be encouraged to return for all subsequent scheduled study visits according to the protocol. Participants who discontinue treatment for latent TB prematurely or who are noncompliant with therapy must immediately discontinue further administration of study intervention and be encouraged to return for all subsequent scheduled study visits according to the SoA (Section 1.3).

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, and PQC, from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

For study intervention that meets the definition of a combination product, malfunctions or deficiencies of a device constituent will be reported as PQC.

Further details on AEs, SAEs, and PQC can be found in Appendix 10 [Section 10.10], Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety.

Serious Adverse Events

All SAEs, as well as PQC, occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Serious adverse events, including those spontaneously reported to the investigator by the final safety visit, must be reported using a serious adverse event form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

A possible Hy's Law case is defined by the occurrence of ALT or AST ≥ 3xULN together with total bilirubin ≥ 2xULN or INR > 1.5 (if measured). Any possible Hy's Law case is considered an important medical event and should be reported to the sponsor in an expedited manner using the Serious Adverse Event form, even before all other possible causes of liver injury have been excluded.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

Solicited Adverse Events

Solicited AEs are predefined local at the injection site and systemic events for which the participant is specifically questioned.

Unsolicited Adverse Events

Unsolicited AEs are all AEs for which the participant is not specifically questioned.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the adverse event, serious adverse event, or PQC as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 10 [Section 10.10], Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all SUSARs. The investigator (or sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

8.3.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using an SAE reporting form. Any participant who becomes pregnant during the study must discontinue further study intervention.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required (see Appendix 5 [Section 10.5], Contraceptive and Barrier Guidance and Collection of Pregnancy Information and Appendix 10 [Section 10.10, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting).

8.3.6. Disease-Related Events and Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

Flares of lupus activity, including LN (defined as an increase in proteinuria and/or serum creatinine concentration, abnormal urine sediment or a reduction in creatinine clearance rate as a result of active disease requiring a change in an immunomodulatory medication for LN beyond that which is outlined in Section 6.5), that meet the definition of an SAE will be reported to the sponsor but will not be reported to the Heath Authorities during the trial so that blinding may be retained in order to ensure study integrity.

8.3.7. Adverse Events of Special Interest

Any newly identified malignancy or case of active TB occurring after the first study intervention administration(s) in participants in this clinical study must be reported by the investigator to the sponsor or designee within 24 hours after being made aware of the event, according to the procedures in Appendix 10 (Section 10.10), Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting, for SAEs. Investigators are also advised that active TB is considered a reportable disease in most countries. These events are to be considered serious only if they meet the definition of an SAE.

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than 10% above the highest dose at a single dosing visit specified in this protocol will be considered an overdose. The sponsor does not recommend specific intervention for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the medical monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities.
- Document the quantity of the excess dose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Serum samples will be used to evaluate the PK of guselkumab, as well as the immunogenicity of guselkumab (antibodies to guselkumab). Serum collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. In addition, 24-hour urine samples will be used to evaluate the potential renal excretion of guselkumab. Participant confidentiality will be maintained.

8.5.1. Evaluations

Venous blood samples of approximately 5 mL will be collected for measurement of serum concentrations of guselkumab and antibodies to guselkumab at the timepoints shown in the SoA (Section 1.3).

Urine samples will be collected for measurement of guselkumab according to the SoA (Section 1.3).

Venous blood samples will be collected and each serum sample will be divided into 3 aliquots (1 each for PK, anti-guselkumab antibodies, and a back-up). Samples collected for analyses of guselkumab serum concentration and antibody to guselkumab may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period, for further characterization of immunogenicity or for the evaluation of relevant biomarkers. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained. Additional information about the collection, handling, and shipment of biological samples can be found in the laboratory manual.

8.5.2. Analytical Procedures

Pharmacokinetics

Serum and urine samples will be analyzed to determine concentrations of guselkumab using a validated, specific, and sensitive immunoassay method by or under the supervision of the sponsor. The sponsor, or its designee, under conditions in which the participants' identity remains blinded, will assay these samples.

8.5.3. Pharmacokinetic Parameters and Evaluations

Parameters

Based on the individual plasma concentration-time data, using the actual dose taken and the actual sampling times, PK parameters and exposure information of guselkumab will be derived using population PK modeling if data permits. Baseline covariates (eg, body weight, age, sex, CrCL, race) may be included in the model, if relevant.

Pharmacokinetic/Pharmacodynamic Evaluations

If data permit, the relationships between serum guselkumab concentration and selected efficacy or PD measures may be analyzed graphically.

8.6. Pharmacodynamics

Pharmacodynamic markers will be evaluated using blood and urine samples collected at visits as indicated in the SoA (Section 1.3). Postbaseline PD test results will not be released to the investigators by the central laboratory.

8.7. Genetics

A pharmacogenomic blood sample will be collected from participants who consent separately to this component of the study to allow for pharmacogenomic research, where local regulations permit. Participation in pharmacogenomic research is optional.

Genetic (DNA) variation may be an important contributory factor to interindividual variability in drug response and associated clinical outcomes. Genetic factors may also serve as markers for disease susceptibility and prognosis and may identify population subgroups that respond differently to an intervention.

8.8. Biomarkers

Biomarker assessments will be made to examine the biologic response to treatment and to identify biomarkers that are relevant to guselkumab treatment and/or LN, where local regulations permit. Assessments (detailed below) will include the evaluation of relevant biomarkers in serum, whole blood, and urine collected as specified in the SoA (Section 1.3), where local regulations permit.

Data collected from these samples will be used for exploratory research that will include the following objectives:

1. To understand the molecular effects of guselkumab.
2. To understand LN pathogenesis.
3. To understand why individual participants may respond differently to guselkumab.
4. To understand the impact of treatment with guselkumab on kidney or systemic inflammation.
5. To develop diagnostic tests to identify LN or SLE populations that may be responsive or non-responsive to treatment with guselkumab.

8.8.1. Serum-based Biomarkers

Blood samples for serum-based biomarker analyses will be collected from all participants, where local regulations permit. Serum will be analyzed for levels of specific proteins, autoantibodies, and other inflammation-related molecules and/or disease-associated serologies relevant to LN and SLE pathogenesis and treatment and response to guselkumab.

8.8.2. Whole Blood-based Biomarkers

Whole blood will be collected by venipuncture from participants for RNA expression analysis, where local regulations permit. Total RNA will be isolated and used for differential gene expression analyses to identify gene expression patterns that are relevant to guselkumab treatment and/or LN and SLE, and to evaluate markers that can predict clinical response. Transcriptome studies will be conducted using microarray, and/or alternative equivalent technologies, which

facilitates the simultaneous measurement of the relative abundances of multiple RNA species resulting in a transcriptome profile for each blood sample. This will enable the evaluation of changes in transcriptome profiles that may correlate with biological response relating to LN or SLE and/or the action of guselkumab.

Whole blood will also be collected and processed for PBMC isolation and cryopreserved for later analysis. Analysis may include but is not limited to flow cytometric assessment of cell populations, single cell transcriptomics, or functional assessment of cells in response to guselkumab treatment.

8.8.3. RNA Expression Research of a Subset of RNA Species

Urine will be analyzed for soluble proteins that may enable the identification of markers related to LN or SLE disease activity and markers associating with guselkumab treatment or response to treatment (from select sites). Cells isolated from the urine sample will be cryopreserved and may later be examined by single cell transcriptomics to identify signatures associating with LN or SLE pathogenesis and signatures associating with guselkumab treatment or response to treatment.

8.8.4. Stopping Analysis

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

8.9. Immunogenicity Assessments

Antibodies to guselkumab will be evaluated in serum samples collected from all participants according to the SoA. Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Serum samples will be screened for antibodies binding to guselkumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to guselkumab and/or further characterize the immunogenicity of guselkumab.

Serum samples will be used to evaluate the immunogenicity of anti-guselkumab antibodies. Samples collected for immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Analytical Procedures

The detection and characterization of antibodies to guselkumab will be performed using a validated assay method by or under the supervision of the sponsor. All samples collected for detection of antibodies to guselkumab will also be evaluated for guselkumab serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for

their ability to neutralize the activity of the study intervention(s). Samples may be stored up to 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to guselkumab.

8.10. Medical Resource Utilization and Health Economics

Not applicable.

9. STATISTICAL CONSIDERATIONS

Due to the sponsor's decision to terminate the study early, some analyses described below may not be performed. The primary efficacy analysis and most secondary efficacy analyses will be performed. All safety analyses will be performed.

For informational purposes, the below section outlines the original statistical plan.

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below.

Specific details will be provided in the revised SAP.

9.1. 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.

9.2. Sample Size Determination

The original design of the study 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.

It should be noted that the sample size determination below was calculated assuming approximately 60 participants would be randomized in this study.

The study will be considered a success if the 1-sided p-value from the difference in proportion of participants with ≥50% decrease in proteinuria between the guselkumab and placebo intervention groups from a logistic mixed effect repeat measurement (MMRM) longitudinal model is less than a 1-sided alpha of 10%.

Table 7 shows the sensitivity of 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 7: 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.

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who signed the ICF.
Full Analyses Set (FAS)	All participants who were randomized in the study and received at least one administration of study intervention.
Full Analyses Set (FASC24)	All participants who were randomized in the study and received at least one administration of study intervention and have the opportunity to complete the Week 24 visit prior to study termination.
Full Analyses Set (FASC52)	All participants who were randomized in the study and received at least one administration of study intervention and have the opportunity to complete the Week 52 visit prior to study termination.
Evaluable	All FAS participants with a baseline measurement.
Safety Analysis Set (SAS)	All participants who received at least one dose of study intervention.
Immunogenicity Analysis Set (IAS)	All participants who received at least 1 administration of guselkumab and have at least one post-dose sample collection.
PK Analysis Set (PKAS)	All participants who received at least 1 administration of guselkumab and have at least one post-dose sample collection.
PD Analysis Set (PDAS)	All participants who received at least 1 administration of study intervention and have at least one post-dose sample collection.

9.4. Statistical Analyses

The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the more important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

Data primarily will be summarized using descriptive statistics. Continuous variables will be summarized using the number of observations, mean, standard deviation (SD), median, interquartile range, minimum and maximum, as appropriate. Categorical values will be

summarized using the number of observations and percentages as appropriate. Median time will be reported for time to event variables. In addition, graphical data displays (eg, line plots) and participant listings may also be used to summarize/present the data.

For continuous endpoints, MMRM (with the Huber-White sandwich estimator) and Analysis of Covariance will be used for analysis. For binary endpoints, logistic regression (MMRM or parametric longitudinal models) and/or the Cochran Mantel Haenszel test will be used to analyze data. For time to event data, log-rank tests will be used to analyze the data.

In general, all statistical tests will be performed at a nominal 1-sided significance level of α 0.10. No multiplicity adjustment will be made for the endpoints being tested.

9.4.2. Primary Endpoint(s)

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

Primary endpoint analysis

Analyses of the primary efficacy endpoint (≥50% decrease in proteinuria from baseline at Week 24) will include data from all randomized participants who received at least one administration of study intervention based on their assigned intervention group, regardless of the actual intervention received and have baseline data (Evaluable population).

Treatment Failure Criteria may include: initiation or increased use of a glucocorticoid or other immunosuppressive agents, however these will be further defined in the SAP.

Participants who meet any of the TF criteria defined in the SAP will be assumed a non-responder, ie, did not meet the ≥50% decrease in proteinuria criteria at Week 24.

The primary analysis will be based on the composite estimand where participants meeting TF criteria are assumed non-achievers from the point of TF forward, and missing data are assumed as non-achievers as well.

The study will be considered a success if the 1-sided p-value from the difference in proportion of participants with ≥50% decrease in proteinuria between the guselkumab and placebo intervention groups from a logistic MMRM longitudinal model is less than a 1-sided alpha of 10%.

See the SAP for further details about the analysis of the primary endpoint, including sensitivity and subgroup analyses.

9.4.3. Secondary Endpoint(s)

Major secondary endpoints include:

1. Proportion of participants achieving 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 CRR.
8. Time to TF.

Secondary endpoint analyses

The Evaluable population will be used for analysis and participants will be counted in the intervention group assigned, regardless of the study intervention received.

Treatment failure and missing data will be included in the secondary endpoint estimands as non-achievers or non-responders.

The details of the analysis of the major secondary endpoints will be included in the SAP.

9.4.4. Tertiary/Exploratory Endpoint(s)

Tertiary Endpoints

Extra Renal Lupus Manifestations

1. Proportion of participants with ≥4-point improvement at Week 24 in 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 CLASI scores at Week 24.

Health-Related Quality of Life and Fatigue

1. Change from baseline in LupusQoL individual domains at Week 24.
2. Change from baseline in FACIT-Fatigue score at Week 24.
3. Change from baseline in lupus symptoms (joint pain, joint stiffness, rash, and swelling [peripheral edema]) at Week 24.
4. PGIC - Change in LN (health condition) at Week 24 and Week 52.

Further details of tertiary and exploratory endpoints analyses will be provided in the SAP.

9.4.5. Long-Term Extension Exploratory Endpoints

1. Proportion of participants maintaining CRR at Week 152.
2. Changes in PRO assessments including LupusQOL, FACIT-Fatigue, lupus symptoms, and PGIC over time during the long-term extension.

9.4.6. Safety Analyses

All safety analyses will be analyzed using the SAS population (refer to Section 9.3 for definition).

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities. Any AE occurring at or after the initial administration of study intervention is considered to be treatment-emergent. All reported treatment-emergent AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group. In addition, comparisons between intervention groups will be provided if appropriate.

The following analyses of AEs will be used to assess the safety of participants:

- Frequency and type of AEs.
- Frequency and type of SAEs.
- Frequency and type of reasonably related AEs as assessed by the investigator.
- Frequency and type of AEs leading to discontinuation of study intervention.
- Frequency and type of infections, serious infections, and infections requiring oral or parenteral antimicrobial treatment.
- Frequency and type of AEs temporally associated with an infusion.
- Frequency and type of injection-site reactions.

Summaries, listings, datasets, or participant narratives may be provided through Week 24 and Week 60 by treatment intervention, for the above AEs, deaths, and severe AEs. Selected safety summaries will also be performed for participants of the LTE (Section 9.4.8).

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test over time, and by treatment intervention. CTCAE toxicity grades (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled timepoint.

The following summaries of clinical laboratory tests will be used to assess participant safety:

- Laboratory parameters and change from baseline in laboratory parameters (hematology and chemistry).
- Summary of maximum CTCAE toxicity grade for postbaseline laboratory values (hematology and chemistry).

Listings of participants with any abnormal postbaseline laboratory values of CTCAE Grade ≥2 will also be provided.

Vital Signs

Blood pressure (systolic and diastolic) will be summarized over time, using descriptive statistics and/or graphically. The percentage of participants with values beyond clinically important limits will be summarized.

9.4.7. Other Analyses

Pharmacokinetic Analyses

Data will be listed for all participants with available serum concentrations. Participants will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study intervention; missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All participants and samples excluded from the analysis will be clearly documented in the study report.

Serum guselkumab concentrations will be summarized over time for all participants who receive at least 1 dose of guselkumab. Descriptive statistics will be calculated at each sampling timepoint.

Urine guselkumab concentrations 24-hrs prior to and after the first IV administration of guselkumab will be summarized in a separate report.

If feasible, population PK analysis of serum concentration-time data of guselkumab may be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline participant characteristics (demographics, laboratory variables, genotypes, race, etc.) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

Immunogenicity Analyses

The incidence of anti-guselkumab antibodies will be summarized for all participants who receive at least 1 dose of guselkumab and have appropriate samples for detection of antibodies to guselkumab (ie, participants with at least 1 sample obtained after their first dose of guselkumab).

A listing of participants who are positive for antibodies to guselkumab will be provided. The maximum titers of antibodies to guselkumab will be summarized for participants who are positive for antibodies to guselkumab.

The incidence of neutralizing antibodies (NAbs) to guselkumab will be summarized for participants who are positive for antibodies to guselkumab and have samples evaluable for NAbs to guselkumab.

Other immunogenicity analyses may be performed to further characterize the immune responses that are generated.

Biomarkers Analyses

Planned biomarker analyses may be deferred if emerging study data show no likelihood of providing useful scientific information. Any biomarker samples received by the contract vendor or sponsor after the cutoff date will not be analyzed, and therefore, excluded from the biomarker analysis.

Changes in serum protein analytes may be summarized for the induction period and summarized by treatment group for the maintenance period. Associations between baseline levels and changes from baseline in select markers and response to treatment may be explored. RNA analyses from cells in blood or urine may be summarized in a separate technical report.

The biomarker analyses will characterize the effects of guselkumab to identify PD markers and biomarkers relevant to treatment, and to determine if these markers can predict response to guselkumab. Results of serum, whole blood analyses, and urine analyses may be reported in a separate technical report.

Pharmacokinetic/Pharmacodynamic Analyses

The relationship between serum concentrations of guselkumab and the efficacy measures and/or relevant PD endpoints may be explored graphically when appropriate. If any visual trend is observed, additional analysis may be conducted if deemed necessary, and will be summarized in a separate report if performed.

Pharmacogenomic Analyses

Genetic (DNA) analyses will be conducted only in participants who sign the consent form to participate in the pharmacogenomic sampling. These analyses are considered exploratory and may be summarized in a separate technical report.

DNA samples will be analyzed for identification of genetic factors that may be associated with clinical response. This research may consist of the analysis of 1 or more candidate genes, assessment of SNPs or genetic modifications, or analysis of the entire genome (as appropriate) in relation to guselkumab intervention and/or LN. Whole blood samples of approximately 30 mL will be collected for genetic analyses as specified in the SoA (Section 1.3).

9.4.8. Long-Term Extension

The LTE begins after the assessments have been completed at Week 52, and will continue until end of study (see Section 4.1.3).

The objective of the LTE is to evaluate the efficacy and safety of long-term guselkumab treatment.

Assessments during the LTE described below will be summarized by treatment group as specified in the SoA (Section 1.3) if data permits:

- Selected efficacy assessments including proportion of participants maintaining CRR through Week 152.

- Changes in PRO assessments including LupusQOL, FACIT-Fatigue, lupus symptoms, and PGIC over time during the long-term extension.
- Selected safety data including analyses of AEs, clinical laboratory tests, and vital signs.
- Serum guselkumab concentrations and antibodies to study intervention.
- Selected biomarkers.

Details of the analyses planned for the LTE will be described in the SAP.

9.5. Data Monitoring Committee or Other Review Board

An external, independent DMC (consisting of at least 2 physician and at least 1 statistician), will be established to monitor safety data on an ongoing basis until all participants reach the Week 52 visit or terminate the study prior to the Week 52 visit.

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 content of the safety summaries, the DMC's role and responsibilities, the general procedures (including communications), and their recommendations on the study conduct are defined and documented in the DMC charter, which will be finalized prior to the first DMC review.

In addition, during the study, the sponsor's study responsible physician (or designee) will regularly review blinded safety data from the sites and notify the DMC and appropriate sponsor personnel of any issues.

The inclusion and exclusion criteria will be adjudicated prior to enrollment. The adjudicated assessment by the sponsor or designee will be the final determinant for allowing enrollment.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

6-MP	6-mercaptopurine
ACTH	adrenocorticotropic hormone
AE	adverse event
ACE	angiotensin-converting enzyme
ACR	American College of Rheumatology
ALT	alanine aminotransferase
ANA	antinuclear antibody
APS	antiphospholipid syndrome
ARB	angiotensin II receptor blocker
AST	aspartate aminotransferase
AUC	area under the curve
AZA	azathioprine
BCG	Bacille-Calmette-guérin
BSA	body surface area
C	complement
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CLE	cutaneous lupus erythematosus
ClinRO	clinician-reported outcome
C_{max}	maximum observed concentration
COVID-19	Coronavirus Disease 2019
CRR	complete renal response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
DBL	database lock
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
dsDNA	double-stranded deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
eGFR	Estimated Glomerular Filtration Rate
eC-SSRS	electronic Columbia-Suicide Severity Rating Scale
ELISA	enzyme-linked immunosorbent assay
EU	European Union
EULAR	European League Against Rheumatism
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full Analyses Set
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRQoL	Health-Related Quality of Life
HRT	hormonal replacement therapy
HS	hidradenitis suppurativa
IA	intra-articular
IAS	Immunogenicity Analysis Set
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
IL	interleukin
IM	intramuscular
IPPI	Investigational Product Preparation and Administration Instructions

IRB	Institutional Review Board
ISN	International Society of Nephrology
IV	intravenous
IWRS	interactive web response system
LB	lower bound
LN	lupus nephritis
LTE	long-term extension
LupusQoL	Lupus Quality of Life
mAb	monoclonal antibody
MMF	mycophenolate mofetil
MMRM	mixed effect repeat measurement
MPA	mycophenolic acid
MTX	methotrexate
NAbs	neutralizing antibodies
NOAEL	no observed adverse effect level
NSAID	nonsteroidal anti-inflammatory drug
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PDAS	PD Analysis Set
PFS	prefilled syringe
PFS-U	PFS in an UltraSafe Plus™ Passive Needle Guard
PFS-Y	PFS with YpsoMate autoinjector
PGA	Physician's Global Assessment
PGIC	Patient Global Impression of Change
PK	pharmacokinetic(s)
PKAS	PK analysis set
PO	orally
PRO	patient-reported outcome(s) (paper or electronic as appropriate for this study)
PsA	psoriatic arthritis
q4w	every 4 weeks
q8w	every 8 weeks
RA	rheumatoid arthritis
RNA	ribonucleic acid
RPS	Renal Pathology Society
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Safety Analysis Set
SC	subcutaneous
SD	standard deviation
SLE	systemic lupus erythematosus
SLEDAI-2K	systemic lupus erythematosus disease activity index 2000
SNP	single nucleic polymorphisms
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	half-life
TB	tuberculosis
TF	Treatment Failure
TH	T-helper
T_{max}	time to maximal concentration
TNF	tumor necrosis factor
UC	ulcerative colitis
ULN	upper limit of normal
UPCR	Urine Protein to Creatinine Ratio
US	United States
WBC	white blood cells

10.2. Appendix 2: 2019 EULAR/ACR Classification Criteria

Entry criterion
Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria
Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous OR discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria >0.5g/24h	4
Renal biopsy Class II or V lupus nephritis	8
Renal biopsy Class III or IV lupus nephritis	10

Immunology domains and criteria	Weight
Antiphospholipid antibodies	
Anti-cardiolipin antibodies OR	
Anti-β2GP1 antibodies OR	
Lupus anticoagulant	2
Complement proteins	
Low C3 OR low C4	3
Low C3 AND low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody* OR	
Anti-Smith antibody	6

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

10.3. Appendix 3: Tuberculin Skin Testing

Administering the Mantoux Tuberculin Skin Test

The Mantoux tuberculin skin test (CDC, 2000) is the standard method of identifying persons infected with *Mycobacterium tuberculosis*. Multiple puncture tests (Tine and Heaf) should not be used to determine whether a person is infected because the amount of tuberculin injected intradermally cannot be precisely controlled. Tuberculin skin testing is both safe and reliable throughout the course of pregnancy. The Mantoux tuberculin test is performed by placing an intradermal injection of 0.1 mL of tuberculin into the inner surface of the forearm. The test must be performed with tuberculin that has at least the same strength as either 5 tuberculin units (TU) of standard purified protein derivative (PPD)-S or 2 TU of PPD-RT 23, Statens Seruminstitut, as recommended by the World Health Organization. PPD strengths of 1 TU or 250 TU are not acceptable (Menzies, 2000). Using a disposable tuberculin syringe with the needle bevel facing upward, the injection should be made just beneath the surface of the skin. This should produce a discrete, pale elevation of the skin (a wheal) 6 mm to 10 mm in diameter. To prevent needle-stick injuries, needles should not be recapped, purposely bent or broken, removed from disposable syringes, or otherwise manipulated by hand. After they are used, disposable needles and syringes should be placed in puncture-resistant containers for disposal. Institutional guidelines regarding universal precautions for infection control (eg, the use of gloves) should be followed. A trained health care worker, preferably the investigator, should read the reaction to the Mantoux test 48 to 72 hours after the injection. Participants should never be allowed to read their own tuberculin skin test results. If a participant fails to show up for the scheduled reading, a positive reaction may still be measurable up to 1 week after testing. However, if a participant who fails to return within 72 hours has a negative test, tuberculin testing should be repeated. The area of induration (palpable raised hardened area) around the site of injection is the reaction to tuberculin. For standardization, the diameter of the induration should be measured transversely (perpendicular) to the long axis of the forearm. Erythema (redness) should not be measured. All reactions should be recorded in millimeters, even those classified as negative.

Interpreting the Tuberculin Skin Test Results

In the US and many other countries, the most conservative definition of positivity for the tuberculin skin test is reserved for immunocompromised patients, and this definition is to be applied in this study to maximize the likelihood of detecting latent TB, even though the participants may not be immunocompromised at baseline.

In the US and Canada, an induration of 5 mm or greater in response to the intradermal tuberculin skin test is considered to be a positive result and evidence for either latent or active TB.

In countries outside the US and Canada, country-specific guidelines **for immunocompromised patients** should be consulted for the interpretation of tuberculin skin test results. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

Treatment of Latent Tuberculosis

Local country guidelines **for immunocompromised patients** should be consulted for acceptable antituberculous treatment regimens for latent TB. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

References

Centers for Disease Control and Prevention. Core curriculum on tuberculosis: What the clinician should know (Fourth Edition). Atlanta, GA: Department of Health and Human Services; Centers for Disease Control and Prevention; National Center for HIV, STD, and TB Prevention; Division of Tuberculosis Elimination; 2000:25-86.

Menzies RI. Tuberculin skin testing. In: Reichman LB, Hershfield ES (eds). *Tuberculosis, a comprehensive international approach*. 2nd ed. New York, NY: Marcel Dekker, Inc; 2000:279-322.

10.4. Appendix 4: Hepatitis B Virus (HBV) Screening with HBV DNA Testing

Participants must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total):

- Participants who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) ***are eligible*** for this protocol.
- Participants who test **negative** for surface antigen (HBsAg-) and test **positive** for core antibody (anti-HBc+) ***and*** surface antibody (anti-HBs+) ***are eligible*** for this protocol.
- Participants who test **positive only** for **surface antibody** (anti-HBs+) ***are eligible*** for this protocol.
- Participants who test **positive** for surface antigen (HBsAg+) ***are NOT eligible*** for this protocol, regardless of the results of other hepatitis B tests.
- Participants who test **positive only** for **core antibody** (anti-HBc+) must undergo further testing for the presence of hepatitis B virus deoxyribonucleic acid (HBV DNA) test. If the HBV DNA test is negative, the participant is eligible for this protocol. If the HBV DNA test is positive, the participant is NOT eligible for this protocol. In the event the HBV DNA test cannot be performed, the participant is NOT eligible for this protocol.

These eligibility criteria based on HBV test results are also represented in Table 1 below.

Table 1: Eligibility Based on Hepatitis B Virus Test Results

HEPATITIS B TEST RESULT			STATUS
Hepatitis B surface antigen (HBsAg)	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc total)**	
negative	negative	negative	**Eligible**
negative	(+)	negative	
negative	(+)	(+)	
(+)	negative *or* (+)	negative *or* (+)	**Not eligible**
negative	negative	(+)	**Require testing for presence of HBV DNA***

*If HBV DNA is detectable, the participant is not eligible for this protocol. If HBV DNA testing cannot be performed, or there is evidence of chronic liver disease, the participant is not eligible for the protocol.

For participants who **are not eligible for this protocol due to HBV test results**, consultation with a physician with expertise in the treatment of HBV infection is recommended.

10.5. Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Appendix 10 [Section 10.10] Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)
a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study intervention or concomitant medications (eg, mycophenolate mofetil [MMF]/mycophenolic acid [MPA] in combination with oral hormonal contraceptives), which may reduce the efficacy of the contraceptive method. In female participants who are of childbearing potential and are receiving MMF/MPA, a barrier contraceptive method should be used concurrently with oral hormonal contraception methods (Section 5.1, Inclusion Criterion #17).

c) Male condom and female condom should not be used together (due to risk of failure with friction).

Pregnancy During the Study

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor or designee by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events (SAEs) and must be reported using the Serious Adverse Event Form. Any participant who becomes pregnant during the study must discontinue further study intervention.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

10.6. Appendix 6: CLASI

Cutaneous LE Disease Area and Severity Index (CLASI)

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

activity ← → **damage**

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

Mucous membrane

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

Dyspigmentation

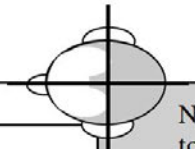
Report duration of dyspigmentation after active lesions have resolved (verbal report by patient – tick appropriate box)

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

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

Alopecia

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



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

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

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

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

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

10.7. Appendix 7: Glucocorticoid Taper

As described in Section 6.5.2, participants are to have their glucocorticoid dose tapered starting from Week 2 down to 5 mg by Week 12. A table showing tapering by the starting prednisone dose is shown below in Table 1.

Table 1: Glucocorticoid Taper Schedule

Week	Taper by Starting Prednisone Equivalent Dose (mg)						
2	60	50	40	30	20	15	10
3	40	30	30	30	20	15	10
4	20	20	20	20	20	15	10
5	20	20	20	20	20	15	10
6	15	15	15	15	15	15	10
7	15	15	15	15	15	15	10
8	10	10	10	10	10	10	10
9	10	10	10	10	10	10	10
10	10	10	10	10	10	10	10
11	10	10	10	10	10	10	10
12	5	5	5	5	5	5	5

10.8. Appendix 8: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the central laboratory:

Protocol Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td rowspan="2">Hematology</td><td>Platelet count
Red blood cell count
Hemoglobin
Hematocrit</td><td><u>Red blood cells (RBC) Indices:</u>
MCV
MCH
% Reticulocytes</td><td><u>White Blood Cell (WBC) count with Differential:</u>
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td colspan="3">Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. A RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.</td></tr>
<tr><td rowspan="2">Clinical Chemistry</td><td colspan="2">Sodium
Potassium
Chloride
Bicarbonate
Blood urea nitrogen (BUN)
Creatinine
Glucose (fasting, or nonfasting, see SoA)
Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic transaminase
Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase
Gamma-glutamyl transferase (GGT)</td><td>Total bilirubin, reflex if abnormal
Alkaline phosphatase
Creatine phosphokinase (CPK)
Lactic acid dehydrogenase (LDH)
Uric acid
Calcium
Phosphate
Albumin
Total protein
Cholesterol
Triglycerides
HDL, LDL, VLDL
Magnesium</td></tr>
<tr><td colspan="3">Details of liver chemistry stopping criteria and required actions and follow-up are provided in Section 10.11: Liver Safety.

Potential Hy's Law case (ALT or AST ≥3 x ULN and Tbili ≥2 x ULN) reporting requirements are defined in Section 8.3.1</td></tr>
<tr><td rowspan="2">Routine Urinalysis</td><td colspan="2"><u>Dipstick</u>
Specific gravity
pH
Glucose
Protein
Blood
Ketones
Bilirubin
Urobilinogen
Nitrite
Leukocyte esterase</td><td><u>Sediment</u>
RBCs
WBCs
Epithelial cells
Crystals
Casts
Bacteria</td></tr>
<tr><td colspan="3">If dipstick result is abnormal, microscopy will be used to measure sediment</td></tr>
</table>

	In the microscopic examination, observations other than the presence of WBC, RBC and casts may also be reported by the laboratory. Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, and urobilinogen will be determined using a dipstick. Red blood cells, WBCs, epithelial cells, crystals, casts, and bacteria will be measured using or microscopy. Crystals, casts and bacteria will only be reported if they are present.
Other Tests	• Urine Pregnancy Testing for women of childbearing potential only (performed locally) • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and Hepatitis B, surface antibody [anti-HBs], Hepatitis B core antibody [anti-HBc], hepatitis C virus antibody, and HCV RNA [if applicable], screening only) • PT, PTT, INR • Anti-dsDNA • Complement - C3, C4 • Antiphospholipid antibodies (anti-cardiolipin immunoglobulin [Ig]G and IgM, anti-β2 glycoprotein IgG and IgM, and lupus anticoagulant) • B-Cell flow cytometry (for those as specified in SoA), screening only • Anti-Smith, anti-Sjögren's-syndrome-related antigen A, anti-Sjögren's-syndrome-related antigen B, anti-ribonucleoprotein • Anti-cyclic citrullinated peptide, Rheumatoid Factor, screening only • Immunoglobulin isotype profile • Antibodies to study intervention – done by sponsor laboratory • 24-hour urine analyses – total volume, creatinine, protein • Hep B DNA • Cystatin C

10.9. Appendix 9: Regulatory, Ethical, and Study Oversight Considerations

10.9.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Clarification Communications

If text within a final approved protocol requires clarification (eg, current wording is unclear or ambiguous) that does not change any aspect of the current study conduct, a protocol clarification communication (PCC) may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, Local Trial Managers (LTMs), Clinical Trial Managers (CTMs), and/or Contract Research Organizations (CROs) who will ensure that the PCC explanations are followed by the investigators.

The PCC Document may be shared by the sites with Independent Ethics Committees/Institutional Review Boards (IECs/IRBs) per local regulations.

The PCC Documents must NOT be used in place of protocol amendments, but the content of the PCC Document must be included in any future protocol amendments.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the

situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated Clinical Trial Agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable

- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)

- Reports of adverse events (AEs) that are serious, unlisted/unexpected, and associated with the study intervention
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.3, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.3.

10.9.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

10.9.3. Informed Consent Process

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing

IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed. The physician may also recontact the participant for the purpose of obtaining consent to collect information about his or her survival status.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

Participants who are rescreened are required to sign a new ICF.

Participants will be asked for consent to provide optional samples for research (where local regulations permit). After informed consent for the study is appropriately obtained, the participant will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the participant.

Where local regulations require, a separate ICF may be used for the required DNA component of the study.

10.9.4. Data Protection

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place.

Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory DNA, PD, biomarker, PK, and immunogenicity research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

10.9.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand guselkumab, to understand LN, to understand differential intervention responders, and to develop tests/assays related to guselkumab and LN. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal From the Use of Research Samples).

10.9.6. Committees Structure

Data Monitoring Committee

Detail regarding the adjudication and DMC are presented in Section 9.5.

10.9.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding guselkumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to

accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of guselkumab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that

questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

10.9.8. Data Quality Assurance

Data Quality Assurance/Quality Control -

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

10.9.9. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in eCRF. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participant's source documents. Data must be entered into eCRF in English. The eCRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All participative measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the electronic data capture (eDC) tool. If corrections to a eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

10.9.10. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; participant diary card, study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable. Given that PROs are reports of a patient's health condition that come directly from the patient, without interpretation by a clinician or anyone else, the responses to PRO measures entered by trial participants into source records cannot be overridden by site staff or investigators.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the eCRF and will be considered source date:

- Race
- History of all nicotine use, eg, cigarettes (including e-cigarettes or the equivalent of e-cigarettes), cigars, chewing tobacco, patch, gum
- Blood pressure and pulse/heart rate
- Height and weight
- Details of physical examination

The following data will be added into the electronic device and will be considered source data:

- PRO
- Physician global assessment of disease activity

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.1.1, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site

- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the eCRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the eCRF.

10.9.11. Monitoring

The sponsor will use a combination of monitoring techniques central, remote, or on-site monitoring to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site, as allowed by local regulation. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

10.9.12. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be

respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.9.13. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

10.9.14. Study and Site Start and Closure

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study/Site Termination

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.10. Appendix 10: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.10.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events (AEs) starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

For combination products with a device constituent, AEs include those resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the device. It includes any adverse event resulting from use error or from intentional misuse of the investigational device.

Serious Adverse Event

A serious adverse event (SAE) based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately

life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

The cause of death of a participant in a study within 12 weeks of the last dose of study intervention, whether or not the event is expected or associated with the study intervention, is considered an SAE.

For combination products with a device constituent, SAEs include adverse device effects that resulted in any of the consequences characteristic of an SAE. An unanticipated serious adverse device effect is a serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report (see Section 2.3. Benefit-Risk Assessment).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For guselkumab, the expectedness of an adverse event will be determined by whether or not it is listed in the IB. For mycophenolate mofetil (MMF), mycopehnoloic acid (MPA), glucocorticoids, ACE inhibitors or ARBs with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the EU SmPC.

10.10.2. Attribution Definitions

Assessment of Causality

The causal relationship to study intervention is determined by the investigator. The following selection should be used to assess all AE.

Related

There is a reasonable causal relationship between study intervention administration and the AE.

Not Related

There is not a reasonable causal relationship between study intervention administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

10.10.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

10.10.4. Special Reporting Situations

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Medication error, intercepted medication error, or potential medication error involving a sponsor medicinal product (with or without patient exposure to the sponsor's medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study intervention from breastfeeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the eCRF.

10.10.5. Procedures

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number

- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon the participant's discontinuation from participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as an SAE, except hospitalizations for the following:

- Hospitalization related to biopsy procedures
- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event
- For convenience the investigator may choose to hospitalize the participant for the duration of the intervention period

Disease progression should not be recorded as an AE or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition (refer to Adverse Event Definitions and Classifications in Appendix 10 [Section 10.10], Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting). Flares of lupus activity, including LN (see Section 4.1.1), that meet the definition of an SAE will be reported to the sponsor but will not be reported to the Heath Authorities during the trial so that blinding may be retained in order to ensure study integrity. Expected progression of disease should not be considered an adverse event (or serious adverse event). However, if determined by the investigator to be more likely related to the study intervention than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study intervention is enhancing disease progression, should be reported per the usual reporting requirements.

Information regarding SAEs will be transmitted to the sponsor using an SAE reporting form, which must be completed and signed by a physician from the study site, and transmitted in a secure manner to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

10.10.6. Product Quality Complaint Handling

Definition

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage, or distribution of the product or the drug delivery system.

This definition includes any PQC related to a device constituent in a combination product, including those used in the administration of the study intervention or the comparator. A device deficiency is an inadequacy of a device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

10.10.7. Contacting Sponsor Regarding Safety, Including Product Quality

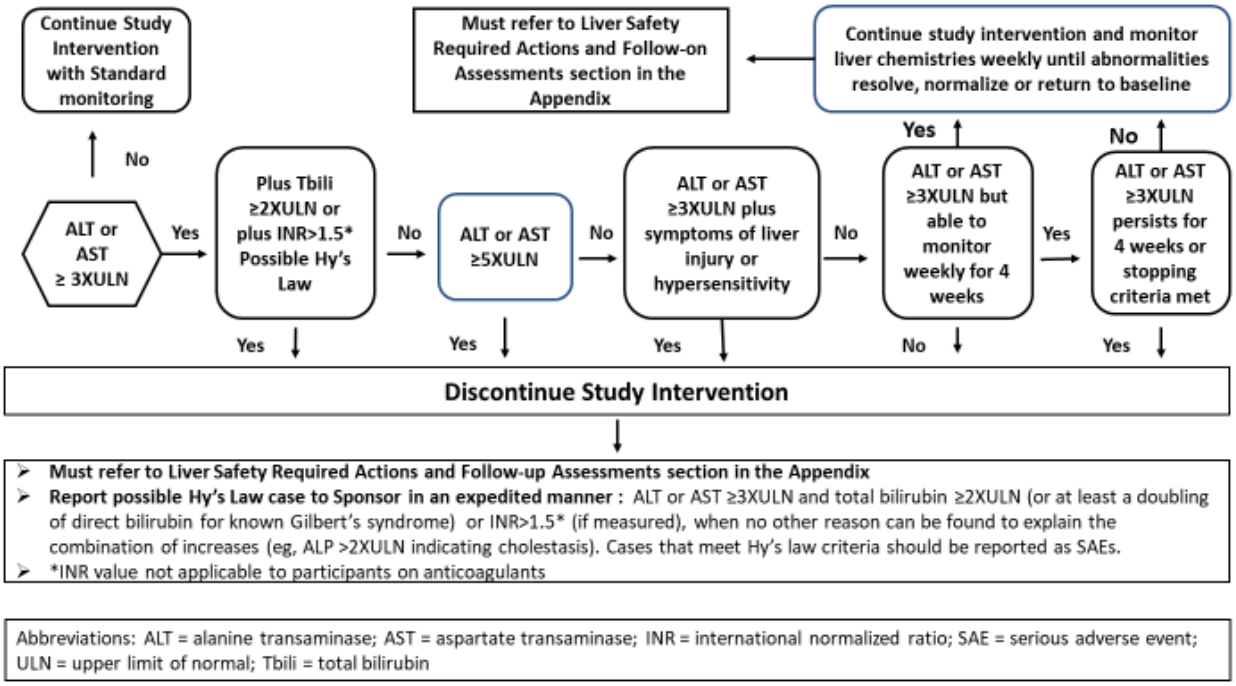
The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues, PQC, or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

10.11. Appendix 11: Liver Safety: Suggested Actions and Follow-up Assessments

10.11.1. Stopping Algorithm

Study intervention will be discontinued for a participant if liver chemistry stopping criteria are met.

Phase 2 Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm (no preexisting liver disease)



Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal; Tbili = total bilirubin

10.11.2. Follow-up Assessments

10.11.2.1. Phase 2 Liver Chemistry Stopping Criteria and Follow-up Assessments

Phase 2 liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology.

Liver Chemistry Stopping Criteria	
ALT/AST--absolute	ALT **or AST-** ≥5xULN
ALT/AST-Increase	**If cannot monitor:** ALT **or AST-** ≥3 xULN and cannot be monitored weekly for 4 weeks **Or if able to monitor:** ALT **or AST-** ≥3xULN persists for ≥4 weeks
Total bilirubin[1, 2]	ALT **or AST-** ≥3xULN **and** total bilirubin ≥2xULN (or at least a doubling of direct bilirubin in known Gilbert's syndrome)
INR[2]	ALT **or AST-** ≥3xULN **and** international normalized ratio (INR) >1.5, if INR measured
Symptomatic[3]	ALT **or AST-** ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Suggested Actions, Monitoring and Follow-up Assessments	
Actions	**Follow-up Assessments**
• **Immediately** stop study intervention • Report the event to the sponsor **within 24 hours** • Complete an SAE form • Perform follow-up assessments as described in the Follow Up Assessment column • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see **MONITORING**) **MONITORING:** **If ALP <2xULN, ALT or AST- ≥3xULN AND total bilirubin ≥2xULN (or at least a doubling of direct bilirubin in known Gilbert's syndrome) or INR >1.5 (if measured):** • Repeat liver chemistry tests (include ALT, aspartate transaminase [AST], alkaline phosphatase, total and direct bilirubin and INR) and perform liver event follow-up assessments within **24 hours** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for pharmacokinetic (PK) analysis after the most recent dose[5] • Obtain serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma-glutamyltransferase [GGT], glutamate dehydrogenase [GLDH], and serum albumin • Fractionate bilirubin • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the CRF as per CRF completion guidelines • Record use of concomitant medications (including

• A specialist or hepatology consultation is recommended **If ALT or AST- ≥3xULN AND total bilirubin <2xULN and INR ≤1.5:** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total and direct bilirubin and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours** • Monitor participant weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline **RESTART/RECHALLENGE** • **If liver event causality is determined to be "not related", restart may be permitted upon written approval of the sponsor**. See restart guidelines	acetaminophen, herbal remedies, recreational drugs and other over-the-counter medications) • Record alcohol use on the CRF as per CRF completion guidelines **<u>If ALT or AST- ≥3xULN AND total bilirubin ≥2xULN or INR >1.5 (if measured)</u>** obtain the following in addition to the assessments listed above**:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins • Serum acetaminophen adduct assay, when available, to assess potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete CRF as per CRF completion guidelines • Liver biopsy may be considered and discussed with local specialist if available: In participants when serology raises the possibility of autoimmune hepatitis (AIH) In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention In participants with acute or chronic atypical presentation • If liver biopsy conducted complete CRF as per CRF completion guidelines

1.Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention if ALT **or AST** ≥3xULN **and** total bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.

2.All events of ALT **or AST-** ≥3 xULN **and** total bilirubin ≥2xULN (or at least a doubling of direct bilirubin in known Gilbert's syndrome), ALT **or AST-** ≥3 xULN **and** INR >1.5 (if measured) may indicate severe liver injury **(possible 'Hy's Law') and must be reported to sponsor in an expedited manner as an SAE**. The INR stated threshold value will not apply to participants receiving anticoagulants.

3.New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
4.Includes: hepatitis A immunoglobulin M (IgM) antibody; HBsAg and HBcAB; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.
5.PK sample may not be required for participants known to be receiving placebo or non-comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated, do not obtain a PK sample. Instructions for sample handling and shipping are in the laboratory manual.

10.12. Appendix 12: Guidance on Study Conduct during the COVID -19 Pandemic

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study-related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If at any time a participant's safety is considered to be at unacceptable risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in-person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation between the participant and investigator, and with the agreement of the sponsor (see below).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance.

If a participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

ADDITIONAL ELEMENTS, WHERE APPLICABLE:

- Certain protocol-mandated visits to the study site may not be possible during the COVID-19 outbreak. Therefore, temporary measures may be implemented if considered appropriate by the sponsor and investigator to maintain continuity of participant care and study integrity. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures:
    - remote (eg, by phone/telemedicine) or in-person, off-site (eg, in-home) interactions between site staff (or designees) and participants for study procedures eg, those related to safety monitoring/efficacy evaluation/study intervention storage and administration (including training where pertinent)

- procurement of study intervention by participants (or designee) or shipment of study intervention from the study site directly to participants for at home administration (including the potential for self-administration of study intervention)
- laboratory assessments using a suitably accredited local laboratory; for selected measures (eg, urine pregnancy), home testing may be employed
- other procedures, eg, imaging, may be conducted at an appropriate facility

- Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).
  - other relevant study data elements impacted by the pandemic should also be documented/labeled as "COVID-19-related" in CRFs and/or other study systems, as directed by detailed sponsor guidance. These may include missed/delayed/modified study visits/assessments/dosing, and instances where temporary measures such as those above are implemented.

- The sponsor will evaluate the totality of impact of COVID-19 on collection of key study data and additional data analyses will be outlined in study SAP(s).
- Precaution: for those who may carry a higher risk for severe COVID-19 illness (eg, those aged over 65 years), follow guidance from local health authorities when weighing the potential benefits and risks of enrolling in the study, and during participation in the study.

10.13. Appendix 13: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 3 [29 March 2022]

Overall Rationale for the Amendment: To revise the inclusion and exclusion criteria on the use of glucocorticoids and cyclophosphamide to better align with standard of care treatment for lupus nephritis and to enhance enrollment in the study without affecting the Sponsor's ability to fulfill the objectives of the study. The requirement for collection of plasma biomarkers samples in the long-term extension (LTE) was removed. In addition, Cystatin C testing is now required. Additional changes are also listed in the amendment table below.

Section number and Name	Description of Change	Brief Rationale
1.1, Synopsis; 4.1.1, Main Study	A sentence was added reporting that participants who experience an LN flare during the main study should discontinue study intervention.	To clarify that participants who experience an LN flare during the main study should discontinue study treatment. In earlier versions of the protocol, this was only included in the LTE section of the protocol.
1.1, Synopsis; 1.3, Schedule of activities; 4.1.1, Main study; 5.1, Eligibility criteria; 5.4, Screen failures; 8, Study Assessments and Procedures	The extension of screening for participants who start with mycophenolate mofetil (MMF)/mycophenolic acid (MPA) at/or within 2 weeks of screening was changed from 2 weeks to 4 weeks.	To allow time for all required screening procedures to occur before the screening window expires for patients newly or recently started on MMF/MPA.
1.1, Synopsis; 1.2, Schema	The sentence specifying which participants may have the option to enroll in the LTE was updated to clarify that participants have to achieve complete renal response (CRR) at Week 48 in addition to Week 52 and have completed the Week 52 assessments to have the option to participate.	The sentence was updated to clarify which participants have the option to enter the LTE.
1.3, Schedule of Activities	A clarification was added when the post-dose 24-hour urine for pharmacokinetic (PK) collection should begin and end relative to the first infusion.	A more detailed instruction was required.
1.3, Schedule of Activities	Plasma biomarker collection was deleted in the LTE.	Plasma biomarker collection was deleted as it was mistakenly listed as a procedure in the LTE in Protocol Amendment 2.
1.3, Schedule of activities; 8, Study Assessments and Procedures	The order of the clinician-reported outcome (ClinRo) procedures was removed.	An order for completion of the ClinRos procedures was not needed.
1.3, Schedule of activities; 10.8, Appendix 8 Clinical Laboratory Tests	Cystatin C was added to list of required laboratory assessments.	The Cystatin C test was added given recent evidence showing that using Cystatin C-based equations for estimating GFR may be more accurate than creatinine-based equations. Use of Cystatin-C based

Section number and Name	Description of Change	Brief Rationale
		equations will not be used in the primary endpoint analysis.
2.1.1, Unmet Need in Lupus Nephritis; 11, References	Belimumab and voclosporin are now mentioned as approved LN medications. The applicable references were added.	To update the section on Unmet Need in LN to reflect that belimumab and voclosporin were approved for the treatment of LN.
2.3.1, Risk for Study Participation; 4.2, Scientific Rationale for Study Design; 5.1, Eligibility criteria	Clarified the inclusion criterion for oral glucocorticoid dosing during the study.	To clarify the required oral glucocorticoid dosing.
2.3.1, Risk for Study Participation; 5.2, Exclusion criteria	The timeframe for receipt of IV cyclophosphamide prior to randomization that would exclude a participant from the study was changed from 6 months to 3 months.	Align with standard clinical practice of patients with LN and duration of biologic effect of prior oral and IV cyclophosphamide with respect to a participant's study eligibility.
3, Objectives and Endpoints	The alternate thresholds for renal response were deleted.	To clarify the definition for complete renal response used in this study.
4.1.1, Main Study; 6.5, Concomitant Therapy; 8.3.6, Disease-Related Events and Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events	The definition of an LN flare was added.	To clarify that the definition of LN flare applies to the main study and the LTE.
5.1, Main Study Inclusion Criteria	The definition of a positive anti-dsDNA antibody level at screening was specified.	To clarify the eligibility criteria for anti-dsDNA antibody level based on central laboratory testing, which aligns with the eligibility for a anti-dsDNA antibody level at screening in other clinical trials in lupus nephritis.
5.1, Main Study Inclusion Criteria	A clarification was added that the participant should have active ISN/RPS proliferative nephritis (with or without Class V membranous nephritis).	An update was needed to clarify that active glomerulonephritis is required for study entry, as opposed to only sclerotic (inactive) lesions.
5.2, Main Study Exclusion Criteria	The term "majority" was removed from the exclusion criteria which states that isolated or predominant Class V LN without coexisting Class III/IV nephritis should be excluded.	It is difficult to quantify which class of LN is dominant and therefore the term "majority" is not applicable.
5.2, Main Study Exclusion Criteria; 6.5.7, Prohibited Therapies	The use of the immunomodulatory agent voclosporin is now specifically mentioned in the exclusion criteria.	Voclosporin is a systemic immunomodulatory agent that is now an approved treatment for lupus nephritis and is prohibited.
5.2, Main Study Exclusion Criteria; 6.5, Concomitant Therapy; 6.5.2, Glucocorticoid Therapy	Participants who have received epidural, IV, or IM administration of glucocorticoids less than or equal to 125 mg/day 6 weeks prior to randomization are now eligible.	To clarify the allowed epidural, IV, or IM glucocorticoids.

Section number and Name	Description of Change	Brief Rationale
5.2, Exclusion Criteria; 6.5, Concomitant Therapy; 6.5.2, Glucocorticoid Therapy	The exclusion criterion regarding the use of high dose, IV corticosteroids was changed.	To allow for the previous use of high-dose, IV corticosteroids that are standard of care for the treatment of lupus nephritis, while also preserving study integrity by excluding the use of high-dose intravenous corticosteroids during screening, which can affect proteinuria levels.
5.2.1, Long-Term Extension Exclusion Criteria	A reference to Section 4.1.1 was added for the definition of an LN flare.	To align the definition of an LN flare within the protocol.
6.5, Concomitant Therapy	The administration of COVID-19 vaccinations and treatments must be recorded.	To align the protocol with the sponsor-related COVID-19 text.
6.5, Concomitant Therapy; 6.5.2, Glucocorticoid Therapy	An updated sentence reporting that changes in any immunomodulatory treatment beyond those allowed per protocol would lead to discontinuation was moved from Section 6.5.2 to 6.5.	The previous sentence in this section only mentioned changes in glucocorticoids which may cause confusion about which changes would lead to discontinuation.
6.5, Concomitant Therapy; 6.5.7, Prohibited therapies	Voclosporin and everolimus were added to the list of prohibited therapies.	Voclosporin and everolimus are systemic immunomodulatory agents and are therefore prohibited per exclusion criterion 23, but were not specifically mentioned previously. Voclosporin was previously an investigational agent but was approved for the treatment of LN during the conduct of the study; the use of it is prohibited during the study.
6.5, Concomitant Therapy; 6.5.3, Nonsteroidal Anti-inflammatory Drugs	A clarification was added that the initiation of NSAID treatment should be avoided.	The initiation of NSAID medications may affect measurement of kidney function and proteinuria.
6.5, Concomitant Therapy; 6.5.4, Anti-hypertensive Medications	A clarification was added that the initiation of treatment with ARB or ACE inhibitors should be avoided.	The initiation of ARB or ACE inhibitors may affect measurement of kidney function and proteinuria.
6.5.2, Glucocorticoid Therapy	"Weeks 2 to 12" was added to the section that describes permitted deviation from the steroid taper.	To specify during which part of the steroid taper the investigator can consider deviating from the taper schedule.
6.5.2, Glucocorticoid Therapy	To clarify that increases above 10 mg/day prednisone equivalent are considered a TF.	To clarify the amount of glucocorticoid increase that would result in a TF.
6.5.2, Glucocorticoid Therapy	A sentence was added that if epidural, IV or IM glucocorticoids are planned, discussion with a medical monitor is recommended.	To ensure that the planned use of epidural, IV, or IM glucocorticoids is acceptable per protocol.
6.5.2, Glucocorticoid Therapy; 10.7 Appendix 7: Glucocorticoid taper	Participants are now required to follow the steroid tapering schedule as closely as possible.	A clarification was needed as there was a discrepancy between the glucocorticoid therapy section, in which it was stated that following the steroid tapering schedule was required, and the glucocorticoid taper appendix in which the

Section number and Name	Description of Change	Brief Rationale
		schedule could be interpreted as a suggestion.
6.5.7, Prohibited Therapies	Sirolimus was removed from the list of calcineurin inhibitors.	Sirolimus was erroneously listed as a calcineurin inhibitor.
6.5.8 Rescue Medications	MTX and AZA/6-MP were removed from the list of rescue medications.	The use of the systemic immunomodulatory agents MTX and AZA/6-MP are prohibited per protocol. There was a discrepancy regarding MTX and AZA/6-MP between Section 6.5.7 (Prohibited Therapies) and Section 6.5.8 (Rescue Medication). The use of the systemic immunomodulatory agents such as MTX and AZA/6-MP are prohibited per Section 6.5.7 of the protocol.
8, Study Assessments and Procedures	Additional information regarding the kidney biopsy for confirming the nephritis was added.	A more detailed instruction was required to clarify that patients with concomitant class V lupus nephritis in addition to class III or IV lupus nephritis are eligible.
8.3.6, Disease-Related Events and Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events;10.10.1, Adverse Event Definitions and Classifications	A sentence mentioning that the cause of death within 12 weeks after the last dose is considered an SAE was moved from Section 8.3.6 to Section 10.10.1.	The sentence was moved to align with the Janssen Research & Development protocol template.
10.10.5, Procedures	A reference to Section 4.1.1, which includes for a definition of LN flare, was added.	A definition of LN flare was added in Section 4.1.1 which is relevant for this section.
10.13, Appendix 13 Protocol Amendment History	The final efficacy visit during the LTE visit was changed from Week 148 to Week 152.	The final efficacy visit was erroneously listed as Week 148 in the Protocol Amendment Summary of Changes Table in Protocol Amendment 2.
Throughout the Protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

Amendment 2 [20 May 2021]

Overall Rationale for the Amendment: To add a long-term extension (LTE) to the study for an additional 2 years in order to evaluate long-term efficacy and safety of guselkumab treatment in lupus nephritis. Eligible participants must have achieved complete renal response (CRR) at Weeks 48 and 52. This amendment also addresses the use of oral contraceptives (using oral contraceptives with a second method of contraception) with concomitant mycophenolate mofetil (MMF)/mycophenolic acid (MPA) due to changes in their label. Additional changes are also listed on the amendment table below.

Section number and Name	Description of Change	Brief Rationale
An LTE is being added for the Phase 2 study.		
Synopsis Overall Design; Synopsis Objectives and Endpoints; 1.2, Schema; 3 Objectives and Endpoints; 4.1.1, Main Study; 4.1.2, Long-Term Extension	Section 4.1.2 was added to the protocol to describe the long-term extension, including details on objectives, eligibility, self-administration, study blind, and final database lock. The initial 60-week study was designated as the "main study". An endpoint regarding serum anti-guselkumab antibodies was updated to include the end of the LTE. A tertiary/exploratory objective was added to evaluate the efficacy of guselkumab in participants with active LN over an extended period with the endpoint of proportion of participants maintaining CRR at Week 152. Added the following tertiary/exploratory PRO endpoint during the LTE: "Changes in PRO assessments including LupusQOL, FACIT-Fatigue, lupus symptoms, and PGIC over time during the long-term extension."	An LTE was added for eligible participants to continue benefitting from study intervention and to obtain longer-term efficacy and safety data.
Synopsis, Intervention Groups and Duration; 6.1.1, Long-Term Extension	Section 6.1.1 was added to specify participants will continue to receive the same study intervention that they were assigned to receive at randomization through Week 48 during the LTE. Participants receiving placebo will be discontinued from study participation after unblinding, and participants receiving guselkumab will continue to receive guselkumab.	To describe study intervention during the LTE.
Synopsis, Statistical Methods; 9.4.5, Long -Term Extension Exploratory Endpoints; 9.4.8, Long-Term Extension	Section 9.4.5 was added to specify LTE exploratory endpoints. Section 9.4.8 was added to specify assessments that will be summarized by treatment group over time during the LTE. Text was added to specify selected safety summaries will be performed for participants in the LTE.	To describe statistical analyses for the LTE.
1.3, Schedule of Activities (SoA)	The title of Table 1 was updated to specify that the table applies to the main study. Footnotes f and g were added to Table 1 (Main Study [Screening through Week 60]) to designate assessments that should occur if participants enter the LTE or complete the Week 52 visit and do not enter the LTE, respectively. Table 2 and Table 3 were added to list the study evaluations that will be performed during the LTE. The LTE begins at Week 52 with study intervention administration occurring every 4 weeks. The final efficacy visit during the LTE is Week 152 and the final safety follow-up visit is Week 160.	Table 2 and Table 3 were added to detail the study visits, efficacy assessments, and safety assessments for participants in the LTE.

Section number and Name	Description of Change	Brief Rationale
	The subsequent tables in the protocol were renumbered accordingly.	
4.4, End of Study Definition	The definition for study completion of the main study was updated to include participants who complete assessments through Week 52 and enter the LTE.	To update the definition of study completion.
5.1, Main Study Inclusion Criteria; 5.1.1, Long-Term Extension Inclusion Criteria; 5.2, Main Study Exclusion Criteria; 5.2.1, Long-Term Extension Exclusion Criteria; 5.3, Lifestyle Considerations	The sections for the original inclusion and exclusion criteria for the study were renamed to the main study inclusion and exclusion criteria. Sections were added for the LTE inclusion and exclusion criteria. For LTE inclusion criteria, 3 criteria were added. For LTE exclusion, 2 criteria were added. Specified the lifestyle considerations for the study includes the LTE and added a lifestyle consideration to be willing and able to complete a participant diary card.	Inclusion and exclusion criteria and lifestyle considerations were added for the LTE.
6.1.2, Combination Products; 6.2 Preparation, Handling, Storage, Accountability	The description of the combination product that will be used in the main study was updated. The description of the combination product that will be used in the LTE was added.	To specify the combination product that will be used during the main study and LTE.
6.3, Measures to Minimize Bias: Randomization and Blinding	Added the blind will be maintained in the LTE until after the last follow-up assessment or study discontinuation for the last participant at Week 60 in the main study.	To specify when the study will be unblinded during the LTE.
6.5, Concomitant Therapy; 6.5.1, Antimalarial Medications; 6.5.2, Glucocorticoid Therapy; 6.5.4, Anti-hypertensive Medications	Requirements for antimalarial medications, glucocorticoid therapy, and anti-hypertensive medications during the LTE were added. In Section 6.5.2, revised the sentence describing short courses of oral glucocorticoids to be 10 days or less.	To specify requirements for concomitant therapies during the LTE. Revised for clarification.
6.7, Continued Access to Study Intervention After the End of the Study	"Main" was added to the following fragment: "At the end of their participation in the main study" Added the Week 48 timepoint to the following fragment: "as determined by meeting CRR at Weeks 48 and 52"	To describe/clarify the timepoint during the study (main and LTE).
7.1.1, Long-Term Extension	Section 7.1.1 was added to specify study intervention will be discontinued if the participant has an LN flare that requires a change in medication during the LTE.	To describe discontinuation of study intervention during the LTE.
8, Study Assessments and Procedures	Under Blood Sample Collection, added the approximate blood volume to be collected from each participant during the LTE from sites collecting biomarkers and from sites not collecting biomarkers.	To specify the approximate amount of blood volume collected during the LTE.
8, Study Assessments and Procedures	Added participant diary card to the list of study-specific materials.	Participants who self-inject study intervention at home during the LTE will record the injection on a diary card.

Section number and Name	Description of Change	Brief Rationale
8.2, Safety Assessments; 8.2.2, Vital Signs	Specified that participants who self-inject at home during the LTE will perform self-evaluation for injection-site reactions and reporting of AEs. Specified that vital signs will only be assessed at study site visits during the LTE.	To specify safety assessments that will be assessed by the participant if study intervention is self-injected at home during the LTE.
10.9.10, Source Documents	Specified "participant" diary card.	Revised for clarification.
Other Revisions in Protocol Amendment 2:		
1.3, Schedule of Activities, Table 1 – Main Study (Screening Through Week 60)	Updated the notes section for the study procedure "Repeat renal biopsy (optional)" and added footnote h to this procedure and to the Urine Analyses (spot urine) assessments at Week 52/Final Efficacy Visit and to Urine protein/creatinine ratio under 24-hour urine analyses at Week 52/Final Efficacy Visit.	Specified the pathology report should be submitted to the sponsor and that urinalysis assessments should not be done within 48 hours after biopsy.
	Footnote e was moved from the Study Procedure column to the Screening (≤8 Weeks) column for chemistry, hematology, and Urine protein/creatinine ratio under Urine Analyses (spot urine).	To clarify that these assessments at Screening must be completed after the participant has received at least 8 weeks of MMF/MPA.
	Added the following text in the notes section for Serum guselkumab concentrations: "that include study intervention administration". Added the following sentence in the notes section for Population PK: "This random sample may not be drawn on the Day 2 visit".	Added notes for clarification.
2.3.1, Risks for Study Participation	Labelled adverse drug reactions were added under Summary of Data/Rationale for Risk for Serious Infections and reactivation of latent infections, Hypersensitivity reactions, including serious hypersensitivity reactions, and Liver injury.	To update the potential risks due to study intervention with the latest safety information for guselkumab
5.1, Main Study Inclusion Criteria; Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information	Text was added to inclusion criterion #17b and to note b under Examples of Contraceptives in Appendix 5 to account for possible mycophenolate and oral hormonal contraceptive interaction.	To minimize the risk of pregnancy since mycophenolate may affect the metabolism of oral contraceptives.
5.2, Main Study Exclusion Criteria	Exclusion criterion #56 note #1 describing exclusion due to recent COVID-19 related features, the reason for screen failure was deleted because it was not relevant.	Note #1 describing exclusion due to recent COVID-19 related features was deleted since the reason for screen failure is exclusion criterion #56.
5.3, Lifestyle Considerations; 6.5.9, Vaccinations (including COVID-19)	Added information on COVID-19 vaccinations to lifestyle considerations and concomitant therapy.	To provide guidance regarding locally approved vaccinations (including emergency use-authorized COVID-19 vaccine).
5.4, Screen Failures, Rescreening	Added a sentence to specify certain assessments from screening could be considered to be complete without repeating for rescreening.	To specify certain assessments from screening could be considered to be complete without repeating for rescreening.
5.4, Screen Failures, Retesting	Added a sentence to specify when Urine Protein to Creatinine Ratio (UPCR) may be retested.	To specify when UPCR may be retested.

Section number and Name	Description of Change	Brief Rationale
7.1, Discontinuation of Study Intervention; 8.2.4, Clinical Safety Laboratory Assessments; 10.8, Appendix 8: Clinical Laboratory Tests; 10.11, Appendix 11: Liver Safety: Suggested Actions and Follow-up Assessments	Removed specific language/details regarding liver function tests in Section 7.1 and replaced with template language that cross-references Appendix 11. Removed specific language/details regarding liver function tests in Section 8.2.4 and Appendix 8, and replaced with template language that cross-references Appendix 11. The title of the Appendix was updated as follows: Liver Safety: Suggested Actions and Follow-up Assessments. The following new subsections were added: 10.11.1, Stopping Algorithm; 10.11.2, Follow-up Assessments; and 10.11.2.1, Phase 2 Liver Chemistry Stopping Criteria and Follow-up Assessments.	The Sponsor's template was updated to provide guidance and evaluations to be obtained in the setting of specific patterns of liver enzymes abnormalities.
8, Study Assessments and Procedures	The following sentence under Screening Phase was bolded: Participants must meet criteria for UPCR, hematology, and chemistry after at least 8 weeks of MMF/MPA.	To emphasize that participants must meet these criteria.
8.1.2, Physician's Global Assessment of Disease Activity	Verbal anchors were updated to "No disease activity" and "Severe disease activity".	Updated the verbal anchors to align with the PGA that is in use for the study.
8.1.6, Patient Global Impression of Change; 11, References.	Revised the description of the Patient Global Impression of Change and updated reference. Added the following reference: Guy W (1976), Ed. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: US Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration, 1976:217-222. The reference list was renumbered accordingly.	Revised for clarification.
8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	A definition was provided to clarify what constitutes a possible Hy's Law case.	Added for clarification.
10.4, Appendix 4: Hepatitis B Virus (HBV) Screening with HBV DNA Testing	Removed the following text from the last bullet point before Table 1: "are Not eligible for this protocol". Provided eligibility criteria for participants who test positive only for core antibody ((anti-HBc+). In Table 1, updated language about eligibility criteria for participants who test positive for core antibody (anti-HBc+) and added a footnote designated with *.	To specify eligibility criteria for participants who test positive for core antibody (anti-HBc+).
10.8, Appendix 8: Clinical Laboratory Tests	Added Hep B DNA as a laboratory parameter under Other Test. Clinical Chemistry footnote description about liver abnormalities was removed and replaced with	Added Hep B DNA as a laboratory parameter. Clinical Chemistry footnote updated to align with the Sponsor's most current version.

Section number and Name	Description of Change	Brief Rationale
	template language that cross-references Appendix 11. Potential Hy's Law case description was added (cross-reference to Section 8.3.1).	
10.9.1, Appendix 10: Regulatory, Ethical, and Study Oversight Considerations	Added text regarding the use of a "Protocol Clarification Communication".	The Sponsor's template was updated to include potential use of a "Protocol Clarification Communication".
10.12, Appendix 12: Guidance on Study Conduct during the COVID-19 Pandemic	Minor edits were made.	Appendix was updated to align with the Sponsor's most current version.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 1 [07 May 2020]

Overall Rationale for the Amendment: It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study. In alignment with recent health authority guidance, the Sponsor is providing options for study related participant management in the event of COVID-19 related disruption to the conduct of the study. Additionally, text defining the combination product was added, as well as updated template text, and other minor changes.

Section Number and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria; 10.12 Appendix 12: Guidance on Study Conduct during the COVID-19 Pandemic	An exclusion criterion related to COVID-19 was added (exclusion #56), and additional information on COVID-19 was added in an appendix.	Clinical study instructions were added to assist sites with the COVID-19 pandemic.
6.1.1 Combination Products	A new subsection was made describing the combination product.	The Sponsor's template was updated to include a description of combination products, and therefore, the Sponsor has updated the text accordingly.
Synopsis: 3 Objectives and Endpoints	An endpoint regarding serum anti-guselkumab antibodies was updated from Week 52 to Week 60	The text was updated to reflect that cumulative data through Week 60 will be used.
Synopsis	Updated text summarizing PROs being assessed.	Clarifying to address the concept that is being assessed with each measure.
Synopsis; 9.4.6 Other Analyses	It was clarified that urine guselkumab concentrations and pharmacokinetic(PK)/pharmacodynamic (PD) additional analyses would be described in separate technical reports.	Clarification was added that urine PK and the PK/PD will be summarized in separate reports and not in the clinical study report.
4.1 Overall Design	Text regarding a futility analysis was deleted.	The Data Monitoring Committee (DMC) will perform periodic safety and efficacy assessments to ensure safety of the subjects and viability of continuing the study.

Section Number and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	A new inclusion (inclusion #23) regarding reading and writing was added.	To align with feedback on patient-reported outcome (PRO) completion.
5.2 Exclusion Criteria	Hemoglobin unit was corrected (exclusion #15).	Minor error was noted.
9.5 Interim Analysis	Text regarding an interim analysis was removed.	The text in this section was duplicative to the text in the section regarding DMC or Other Review Board. The study will not include an interim analysis, rather, a DMC will be reviewing unblinded data which is already described in the section regarding DMC or Other Review Board. This duplicative text was removed to avoid confusion.
10.4 Appendix 4 Hepatitis B Virus (HBV) Screening with HBV DNA Testing	Hepatitis B core antibody testing information was updated.	Updated to align with eligibility critiera.
10.8 Appendix 8 Clinical Laboratory Tests	Clinical chemistry test names were updated	Minor clarifications.
Throughout the protocol	Updates were made to the safety sections based on template language changes. And additional template sentences were added regarding PROs.	The Sponsor's protocol template was updated.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	24-May-2022 16:27:12 (GMT)	Document Approval

Janssen Research & Development *

Clinical Protocol

GUIDANCE ON STUDY CONDUCT DURING MAJOR DISRUPTION

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

ORCHID-LN

A Study of the Efficacy and Safety of Guselkumab in Participants with Active Lupus Nephritis

Protocol CNTO1959LUN2001; Phase 2

CNTO 1959 (guselkumab)

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

EudraCT NUMBER: 2018-003155-38

Status: Approved
Date: 24 May 2022
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-RIM-742336, Version 1.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

STUDY CONDUCT DURING A MAJOR DISRUPTION

GUIDANCE ON STUDY CONDUCT DURING MAJOR DISRUPTION

It is recognized that the major disruption involving Ukraine, Russia, and neighboring countries/territories may have an impact on the conduct of this clinical study due to, for example, isolation or quarantine of participants and study site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being unavailable, isolated, or reassigned to critical tasks.

The sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's travel to the study site is considered to be dangerous, study participation may be interrupted, and study follow-up conducted. If it becomes necessary to discontinue participation in the study, the procedures outlined in the protocol for discontinuing study intervention will be followed.

If, as a result of the major disruption involving Ukraine, Russia, and neighboring countries/territories scheduled visits cannot be conducted in person at the study site, they will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted after consultation with the participant, investigator, and the sponsor.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. Modifications made to the study conduct as a result of the major disruption involving Ukraine, Russia, and neighboring countries/territories should be summarized in the clinical study report.

- Certain protocol-mandated visits to the study site may not be possible during the major disruption involving Ukraine, Russia, and neighboring countries/territories. Therefore, temporary measures may be implemented if considered appropriate by the sponsor and investigator to maintain continuity of patient care and study integrity. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures:
  - remote (eg, by phone/telemedicine) or in person, off-site (eg, in-home) interactions between site staff (or designees) and participants for study procedures eg, those related to safety monitoring/efficacy evaluation/study intervention storage and administration (including training where pertinent)

  - study intervention administration may take place outside of the scheduled visit window, if the investigator determines this to be safe for the participant, due to disruption of study intervention shipment to the site
  - laboratory assessments using a suitably accredited local laboratory

- Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented in the electronic case report form (eCRF).
  - other relevant study data elements impacted by the major disruption involving Ukraine, Russia, and neighboring countries/territories should also be documented in eCRFs and/or other study systems, as directed by detailed sponsor guidance. These may include missed/delayed/modified study visits/assessments/dosing, and instances where temporary measures such as those above are implemented.
- The sponsor will evaluate the totality of impact of the major disruption involving Ukraine, Russia, and neighboring countries/territories on collection of key study data.
  - if needed additional data analyses will be outlined in study statistical analysis plan.

INVESTIGATOR AGREEMENT

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I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the protocol Date: _____
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.