Janssen Research & Development*

Statistical Analysis Plan

A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study of Ustekinumab in Subjects with Active Systemic Lupus Erythematosus

Protocol CNTO1275SLE3001; Phase 3
AMENDMENT 2

STELARA® (ustekinumab)

*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 Infectious Diseases BVBA; Janssen R&D Ireland; 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.

Status:	Approved
Date:	23 September 2020
Prepared by:	Janssen Research & Development
Document No.:	EDMS-ERI-161845442

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

TABLE OF CONTENTS

AMENDMENT HISTORY

DATE	AMENDMENT
23 April 2018	Original STABLE DRAFT Version
31 January 2019	Approved Version 1: Updates to address regulatory response, clarification to endpoints, sensitivity analyses and other analyses
8 January 2020	Amendment 1: Updates to imputation rules for missing AE time to onset. Update to prohibited medication rules. Update to treatment failure rules with inclusion of periodic review text. Updates to address regulatory response, clarifications to endpoints, sensitivity analyses (including tipping point analyses) and supportive analyses, and inclusion of sample SAS® code. Addition of a linear regression supportive analysis. Detailed explanation of glucocorticoid reduction rules. Addition of text addressing handling of data from any site closures.
22 Sep 2020	Amendment 2: Added SLEDAI-2K supportive analyses. Updated for COVID-19 including adding impact assessments, adjustment of analyses and estimands. Due to the planned futility analysis meeting criteria and the trial termination on 26 June 2020, the SAP has reduced efficacy analyses.

ABBREVIATIONS

ACE	angiotensin-converting enzyme
ADA	anti-drug antibody
AE	adverse event
ALT/SGPT	alanine aminotransferase
ANCOVA	analysis of covariance
APAC	Asia Pacific
ARB	angiotensin II receptor blocker
AST/SGOT	aspartate aminotransferase
ATC	anatomic and therapeutic Class
AUC	area under the curve
AZA/6 MP	Azathioprine / 6-mercaptopurine
BILAG	The British Isles Lupus Assessment Group
BMI	body mass index
BSA	body surface area
CI	confidence interval
CLASI	Cutaneous Lupus Erythematosus Disease Activity Index
Cmax	maximum concentration
COVID-19	Coronavirus Disease 2019
CRF	case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
ECG	Electrocardiogram
eCRF	electronic case report form
EEU	Eastern European Union
EMEA	Europe, Middle East and Africa
F (%)	absolute SC bioavailability
FAS	full analysis set
FDA	Food and Drug Administration
HLGT	higher level group term
ICH	International Conference on Harmonization
IN	interim analysis
IQ	Interquartile
IV	Intravenous
IWRS	interactive web response system
LA	Latin America
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified full analysis set
MMF	mycophenolate mofetil
MPA	mycophenolate acid
MTX	Methotrexate
NA	North America
NAb	neutralizing antibodies
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSAIDS	nonsteroidal anti-inflammatory drugs
P/C	protein/creatinine ratio
PD	pharmacodynamic
PI	principal investigator
PK	pharmacokinetic(s)
S2K RI-50	SLEDAI-2K Responder Index

SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SMQs	standardized MedDRA queries
SLE	systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SLICC	Systemic Lupus International Collaborating Clinics
SRI	Systemic Lupus Erythematosus Responder Index
TEAE	treatment-emergent adverse event
Tmax	time to maximum concentration
US	United States
V	volume distribution
VAS	visual analogue scale
Vz	volume of distribution based on terminal phase
Vz/F	apparent volume of distribution based on terminal phase after extravascular administration
WEU	Western European Union
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This Statistical Analysis Plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for all planned analyses of efficacy, safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity of ustekinumab.

The trial was terminated for futility on June 26th 2020, therefore this SAP covers all analyses for the study including analyses for the primary Week 52 DBL as well as those planned for the long term extension (through final Week 176 visit) of the study. As the trial was terminated for meeting futility criteria (see Section 3) efficacy analyses have been reduced to mainly the primary and major secondary endpoints and minimal additional analyses. See SAP Amendment #1, dated January 8th, 2020 for the originally planned analyses, sensitivity analyses and exploratory work.

1.1. Trial Objectives

Primary Objectives

The primary objectives are:

The primary objective is to evaluate the efficacy of ustekinumab in subjects with active Systemic Lupus Erythematosus (SLE) who have not adequately responded to one or more standard of care treatments.

Secondary Objectives

The secondary objectives are to evaluate the following in subjects with active SLE who have not adequately responded to one or more standard-of-care treatments:

- Reduction in SLE flares
- Improvement in global and organ-specific (mucocutaneous, musculoskeletal, etc.) measures of SLE disease activity
- Glucocorticoid sparing

Additional Objectives

The additional objectives are to evaluate:

- Safety and tolerability
- Pharmacokinetics and immunogenicity
- Pharmacodynamic biomarkers and predictive biomarkers to identify subjects most likely to benefit from treatment with ustekinumab
- Measures of low disease activity state, remission, and organ damage
- Effect on health-related quality of life, physical function, and work productivity

1.2. Trial Design

CNTO1275SLE3001 is a multicenter, randomized, double-blind, placebo-controlled, parallel group, study to evaluate the efficacy, safety, and tolerability of ustekinumab in addition to standard-of-care background therapy in subjects between 16 (unless restricted by local requirements) and 75 years of age, inclusive, with active, autoantibody-positive SLE who have not adequately responded to one or more standard-of-care treatments.

The total duration of the study is up to 182 weeks, consisting of 3 study periods: a ≤6-week screening period (re-screening is permitted once per subject), a 52-week double blind period, and a 124-week extension period.

Approximately 500 subjects will be randomly assigned in a 3:2 ratio to receive either ustekinumab or placebo with the following treatment administrations:

- Week 0: Body weight-range based IV administration of ustekinumab (~6 mg/kg) or placebo
- Week 8 and every 8 weeks (q8w) thereafter through Week 48: SC administration of 90 mg ustekinumab or placebo
- Subjects entering the extension period: SC administration of 90 mg ustekinumab q8w through Week 160

A placebo comparator (in addition to standard of care background therapy) will be used in this study through Week 52 to allow for blinded, placebo-controlled evaluation of the long-term efficacy and safety of ustekinumab in subjects with SLE.

Subjects will be stratified by race, presence of lupus nephritis, and a combined factor (baseline SLE medications and clinical SLEDAI-2K score), using permuted block central randomization.

Note that the clinical SLEDAI score stratification factor utilized in the randomization procedure is collected at baseline and therefore baseline laboratory results (part of the total SLEDAI score) are not available. The clinical SELDAI score as defined in the protocol does not include laboratory results or lupus headache. All demographics, efficacy and subgroup analyses will utilize the total SLEDAI score.

The primary efficacy analysis will be performed after all subjects have completed Week 52 efficacy assessments (or discontinued) with additional secondary endpoints to be analyzed at Week 24 and Week 52. After Week 52, eligible subjects may enter the extension period.

Every reasonable effort should be made to keep concomitant medications stable as defined in the protocol, with the exception that glucocorticoid tapering will be instituted between Week 24 and Week 40. Beginning at the screening visit, all concomitant therapies and all changes in concomitant therapies should be recorded throughout the study.

Subjects with cutaneous disease who provide consent will participate in medical photography to evaluate skin photographs at participating study sites.

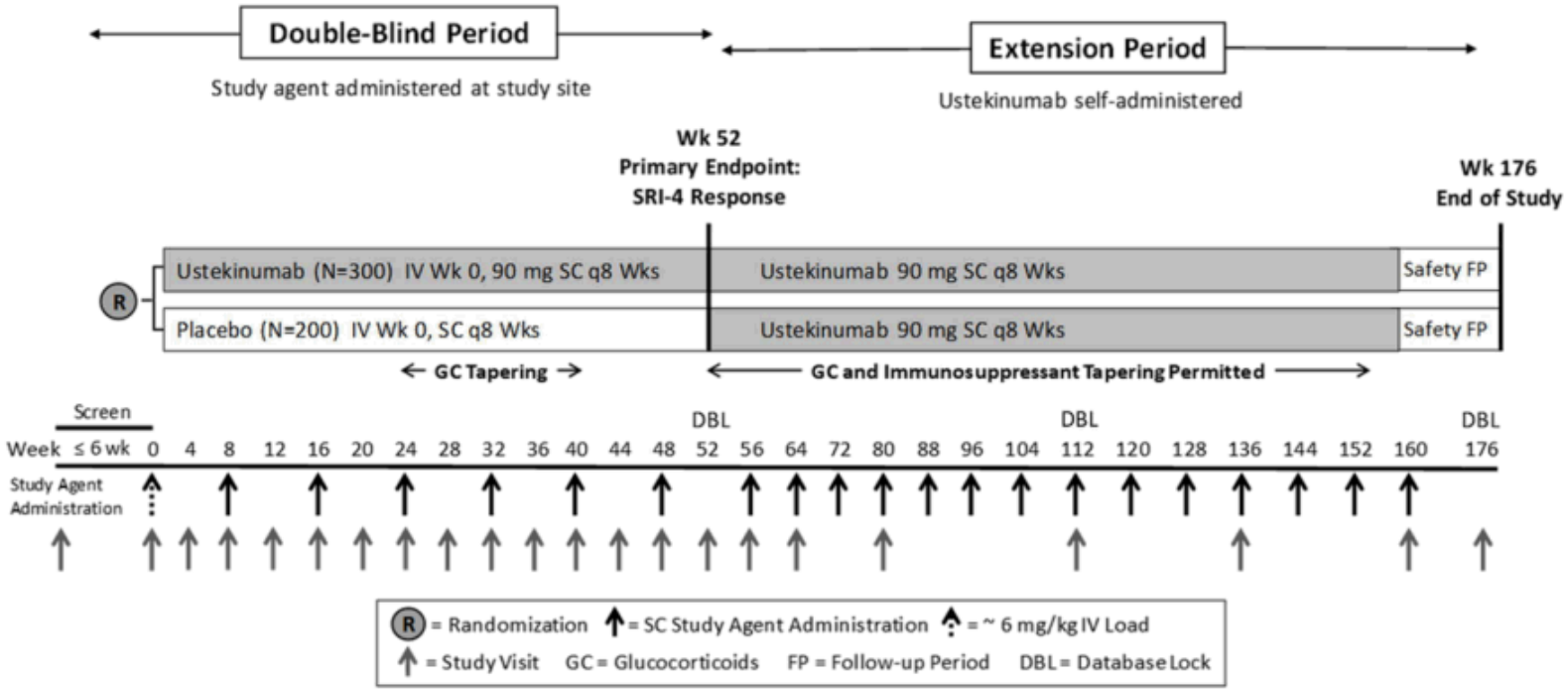
Database locks are planned at Week 52, Week 112, and at Week 176. The end of the study is defined as the last follow-up assessment (16 weeks after the last dose of study agent is administered at Week 160) for the last subject.

An independent Data Monitoring Committee (DMC) will be commissioned for this study.

A futility analysis will be conducted 24 weeks after 50% of the planned subjects have been randomized. The analysis will be performed in an unblinded fashion by the independent DMC based primarily on Week 24 efficacy data. Additional data available at the time of the futility analysis (e.g., other endpoints, other time points) may also be considered.

A diagram of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



1.3. Statistical Hypotheses for Trial Objectives

The primary endpoint of the study is the proportion of subjects achieving a SRI-4 composite response at Week 52.

The statistical hypothesis for the study is that treatment with ustekinumab is superior to placebo in subjects with active SLE who have not adequately responded to one or more standard-of-care treatments as measured by the proportion of subjects achieving a SRI-4 composite response at Week 52.

1.4. Sample Size Justification

The sample size calculation is based upon the primary endpoint, the proportion of SRI-4 composite responders at Week 52. A sample size of 300 subjects treated with ustekinumab and 200 subjects with placebo is projected to give approximately 98% power to detect a significant difference in response rate compared with placebo (assuming 35% and 53% response rates in placebo and ustekinumab, respectively, which translates to 18% absolute increase over placebo or an odds ratio of 2.09) with an alpha (α) level of 0.05. The assumption of a 35% responder rate for placebo is based upon a previous study in which a similar SLE population was treated and is consistent with the results observed in the recent ustekinumab SLE study, CNTO1275SLE2001.[9]

The power to detect a significant treatment difference at $\alpha = 0.05$ (2-sided) is calculated under various assumptions (Table 1).

Table 1: Power to Detect a Significant Treatment Difference in the Proportion of Subjects with SRI-4 Response at Week 52

Proportion of Placebo Group with Response (%)	Absolute Increase in Response (%)	Proportion of Ustekinumab Group with Response (%)	Odds Ratio	Power
20	15	35	2.15	96%
	20	40	2.67	99%
	25	45	3.27	99%
25	15	40	2.00	94%
	20	45	2.45	99%
	25	50	3.00	99%
30	15	45	1.91	93%
	20	50	2.33	99%
	25	55	2.85	99%
35	15	50	1.86	91%
	18	53	2.09	98%
	20	55	2.27	99%
40	25	60	2.79	99%
	15	55	1.83	91%
	20	60	2.25	99%
45	25	65	2.79	99%
	20	65	2.27	99%
	25	70	2.85	99%

*Note: SRI-4 composite response is defined as a ≥ 4-point reduction in SLEDAI-2K score, no new BILAG A and no more than 1 new BILAG B domain score, and no worsening (<10% increase) from baseline in the PGA.[4]

1.5. Randomization and Blinding

Randomization

Central randomization will be implemented in this study using an interactive web response system (IWRS). Subjects will be randomly assigned to 1 of 2 treatment groups based upon a computer-generated randomization schedule prepared before the study under the supervision of the sponsor; however, the sponsor will not be privy to the actual randomization schedule. When a subject is eligible for randomization at a study site, the randomization requestor at that study site will contact the IWRS using the requester's own user identification and personal identification number and provide the relevant subject details to uniquely identify that subject.

Permuted block randomization with the following stratification factors will be used:

- race (white, black, all other categories combined)
- presence of Lupus Nephritis at baseline (Y/N)
- composite of baseline SLE medications and clinical SLEDAI score (high medications and SLEDAI ≥ 10, high medications and SLEDAI < 10, medium medications and SLEDAI ≥ 10, medium medications and SLEDAI < 10)
  - Subjects will be defined as receiving high medications if they are receiving any of the following: ≥ 15 mg/wk MTX, or ≥ 1.5 mg/kg/day AZA/6-MP, or ≥ 1.5 g/day MMF/1.125 g/day MPA, and/or ≥ 15 mg/day prednisolone or equivalent
  - Subjects receiving baseline medication(s) for SLE that do not meet the above criteria for the category of 'high' medications would be included in the 'medium' medication category

Based upon the computer-generated randomization schedule, the IWRS will assign a unique treatment code, which will dictate the treatment assignment and matching study agent kit for that subject. The IWRS will be developed, validated, and administrated by the IWRS vendor.

Approximately 500 subjects will be randomly assigned in a 3:2 ratio to receive either ustekinumab or placebo, respectively. Subjects assigned to the ustekinumab group will receive an initial, body weight-range based IV dose approximating 6 mg/kg of ustekinumab (ustekinumab 260 mg weight ≤55 kg; ustekinumab 390 mg weight >55 kg and ≤85 kg; ustekinumab 520 mg weight >85 kg), and subjects who were randomized to placebo will receive placebo treatment. Starting at Week 8, subjects will receive SC dosing with either placebo or ustekinumab 90 mg q8w through Week 48. Subjects entering the extension period will receive open-label ustekinumab 90 mg SC every 8 weeks through Week 160.

Blinding

The study blind will be maintained for the duration of the study until after the primary Week 52 DBL.

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 subject in emergency situations where unblinding is deemed necessary.

Data that may potentially unblind the treatment assignment (e.g., study agent serum concentrations, anti- ustekinumab antibodies, study agent preparation/accountability data, treatment allocation, 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 database lock and unblinding.

The blind will be maintained during the extension period until the last subject completes the Week 52 evaluations and the 52-week database is locked. At the Week 52 DBL, the data will be unblinded for analysis to the sponsor. Investigative study sites and subjects will remain blinded to initial treatment assignment until after the final database (Study Extension Week 176) is locked.

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. The Investigator may in an emergency determine the identity of the study agent by contacting the IWRS. While the responsibility to break the treatment assignment 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 by the IWRS, in the appropriate section of the case report form (CRF), and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

The external independent DMC and Statistical Support Group (SSG: an external independent team supporting analytical and operational aspects of the DMC as described in the DMC Charter) are unblinded to subject treatment groups. The contents of the unblinded data to which the DMC and SSG have access should not be divulged, in any way, to members of the study team or to any members of the Sponsor Committee unless specifically requested by the Sponsor Committee Chairperson, until the study has completed. The Sponsor Committee Chairperson will only request unblinded data to access safety if absolutely needed and those individuals unblinded to the data will be documented in advance and not directly involved in study conduct. More detailed information is included in the DMC Charter.

Subjects who have had their treatment assignment unblinded should continue to return for scheduled evaluations.

For the specified interim analyses, the randomization codes and the translation of randomization codes into treatment and control groups will be disclosed to those authorized as detailed in the DMC Charter.

1.6. Coronavirus 2019 (COVID-19)

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 subjects and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

On May 8th, 2020 a study specific guidance was created to document approaches that are being implemented to maintain continuity of patient care and minimize risks to trial integrity during the COVID-19 pandemic. These modifications to study procedure were to be implemented on an as-needed (subject-by-subject or site-by-site) basis. More details about study operational procedures related to COVID-19 are described in the guidance and the COVID-19 Appendix to the study protocol.

Note that references throughout the SAP to COVID-19 and any impact it may have on a subject's data handling rules is NOT in reference to the coronavirus disease but instead to operational and logistic issues related to COVID-19 (e.g. inability to access a site for dosing or regularly scheduled visits).

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

Unless otherwise specified, nominal visits will be used for all by visit analyses. The study visits scheduled after randomization should occur at the times delineated in the Time and Events Schedule and the associated COVID-19 study specific guidance.

For PK analyses, if a subject has an administration of study agent more than +/- 7 days of the scheduled dosing date, the concentration data collected between such a dosing visit and the subsequent dosing visit will be excluded from the by-visit data analyses. For the Week 52 visit, if the PK sampling time deviates more than +/- 3 days of the scheduled date of study agent administration, the PK concentration at this visit will be excluded from the by-visit data analyses.

2.2. Pooling Algorithm for Analysis Centers

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

2.3. Analysis Sets

2.3.1. Randomized Analysis Set

The randomized analysis set includes all randomized subjects.

In the demographics and disposition analyses, subjects will be analyzed according to their assigned treatment group.

2.3.2. Efficacy Analysis Set(s)

2.3.2.1. Full Analysis Set

The efficacy analysis set will be based upon the Full Analysis Set (FAS) and includes randomized subjects who received at least 1 dose (partial or complete, IV or SC) of study agent.

In the efficacy analyses, subjects will be analyzed according to their assigned treatment group regardless of their actual treatment received.

Unless otherwise stated, efficacy analyses will be limited to those FAS subjects who should have had a given visit based upon their latest scheduled study visit and the trial termination date of 26th June 2020. To determine the latest visit where a subject should be included in an any analysis, use the following formula:

- Identify the last scheduled and completed visit date for a subject. This will be classified as 'Week A' where 'A' is the numeric visit week.
- Calculate the time from last schedule visit date to trial termination using the following formula:
    - [(trial termination date – last scheduled visit date) + 1] / 7 = value. Decimal places are removed, and the remaining value represents the weeks since last visit up to and including trial termination for a subject. This will be classified as 'B'
- Calculate their derived latest visit as Week (A+B)

The subject would be included in any analysis less than or equal to the derived latest visit above. For example, if a subject had their last scheduled and completed visit on January 20th, 2020, and this was the Week 16 visit for the subject, the following would be their derived latest visit:

- Subjects last scheduled and completed visit was Week 16
- Trial termination date – last visit date: 26 June 2020 minus 20 Jan 2020 + 1 = 169 days
- Weeks since last visit: 169 days / 7 = 24.1 weeks, after removing the decimal this is 24 Weeks
- Subjects derived latest visit is Week 16 + 24 weeks = Week 40

Therefore, for this subject, they would be included through Week 40 in the analysis. They would not be included in any analysis after Week 40.

2.3.3. Safety Analysis Set

The safety analysis set includes all randomized subjects who received at least 1 dose (partial or complete, IV or SC) of study agent.

In the safety analyses, subjects will be analyzed according to the actual treatment received.

2.3.4. Pharmacokinetics Analysis Set

The PK analysis set is defined as subjects who have received at least 1 complete dose of ustekinumab and have at least one valid blood sample drawn for PK analysis.

In the PK analyses, subjects will be analyzed according to the actual treatment received.

2.3.5. Immunogenicity Analysis Set

The immunogenicity analysis set is defined as all subjects who received at least one dose (partial or complete, IV or SC) of ustekinumab and have appropriate samples for detection of antibodies to ustekinumab (i.e. subjects with at least 1 appropriate sample obtained after their first dose of ustekinumab).

In the immunogenicity analyses, subjects will be analyzed according to the actual treatment received.

2.3.6. Pharmacodynamics Analysis Set

The PD analysis set is defined as all subjects who received at least one dose (complete or partial, IV or SC) of study agent. Subjects will be analyzed according to the actual treatment received.

2.4. Definition of Subgroups

To evaluate the consistency of the primary efficacy endpoint (proportion of subjects with SRI-4 composite response at Week 52) subgroup analyses may be performed when the number of subjects in the subset permits (at least 15 subjects for each treatment group within a subset).

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

1. Subgroups defined by demographics
    a. Region (APAC, LA, EEU, Africa, NA, WEU)
    b. Race (White, Black, Asian, All other categories)
    c. Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
    d. Age (16-25, 26-55, Over 55)
    e. Body Weight (≤ 55 kg, > 55 and ≤ 85 kg, > 85 kg)
    f. BMI (Normal [< 25 kg/m^2], Overweight [≥ 25 to < 30 kg/m^2], Obese [≥ 30 kg/m^2])
    g. Sex (Male, Female)
    h. Subjects age at SLE diagnosis (≤ 21 Years, > 21 Years)

2. Subgroups defined by baseline characteristics
    a. Combined factor of baseline SLE Medication (High, Medium) and SLEDAI-2K score (≥ 10, <10)
    b. SLEDAI-2K Score (< Median, ≥ Median)
    c. PGA Score (< Median, ≥ Median)
    d. Presence of lupus nephritis at baseline (Y, N)
    e. Urine Protein/Creatinine Ratio at baseline (< Median, ≥ Median)

f. Serologic status individually and collectively for anti-dsDNA, C3 and C4
   i. dsDNA (positive, negative)
   ii. Complement C3, C4 (normal, abnormal)

g. SLE medication use at baseline

For analysis 2g (SLE medication use at baseline), the following categories will be analyzed given at least 15 subjects for each treatment group within a subset:

SLE Concomitant Medication Therapy at Baseline
Glucocorticoids ONLY
Antimalarials ONLY
Immunosuppressants ONLY
Antimalarials + Glucocorticoids only
Antimalarials + Immunosuppressant only
Immunosuppressants + Glucocorticoids only
Glucocorticoids + Antimalarials + Immunosuppressant

(APAC = Asia Pacific, LA = Latin America, EEU = Eastern European Union, NA = North America, WEU = Western European Union)

2.5. Study Day and Relative Day

The Reference Date is the date of the first study agent administration. If the date of the first study agent administration is missing or the first study agent administration is not done, then the Reference Date equals the corresponding visit date (e.g., Week 0 visit date). If the corresponding visit date is also missing, then the Reference Date equals the randomization date. Study Day 1 or Day 1 refers to the reference date (there is no Study Day 0). All efficacy and safety assessments at all visits will be assigned a day relative to this date.

Study day or relative day for a visit is defined as:

- Visit date - (date of Study Day 1) +1, if visit date is ≥date of Day 1
- Visit date - Date of Day 1, if visit date <date of Day 1

There is no 'Day 0'

2.6. Baseline

Unless otherwise stated, baseline is defined as the last observation prior to the start of the first study agent administration.

2.7. Imputation Rules for Missing AE Date/Time of Onset/Resolution

Partial AE onset dates will be imputed as follows:

- If the onset date of an adverse event is missing day only, it will be set to:
  - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the study agent start
  - The day of study agent start, if the month/year of the onset of AE is the same as month/year of the study agent start date and month/year of the AE resolution date is different
  - The day of study agent start or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the study agent start date and month/year of the AE resolution date are same
- If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is on or after the study agent start date
  - Month and day of the study agent start date, if this date is the same year that the AE occurred
  - Last day of the year if the year of the AE onset is prior to the year of the study agent start date,
  - The AE resolution date.
- Completely missing onset dates will not be imputed.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an adverse event is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the day of the date of death, if the death occurred in that month.
- If the resolution date of an adverse event is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year.
- Completely missing resolution dates will not be imputed.

AE onset/resolution dates with missing times will be imputed as follows:

- A missing time of onset of an adverse event will be set to:
  - 00:01 if the onset date does not occur on the same day as a study agent administration.
  - The start time of the corresponding study agent administration if onset date does occur on the same day as study agent administration.
- The missing time of resolution of an adverse event will be set to 23:59.

If a missing time is associated with a partial or missing date, the date will be imputed first prior to imputing the time.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

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

The follow offers a high-level summary of Interim Analysis activities.

3.1. Interim Analysis

The interim analysis will be performed 24 weeks after 50% of the planned subjects have been randomized. This is expected to be approximately a year and a half after the first subject is dosed.

The objective of the Interim Analysis is to decide whether to terminate the study for futility, by evaluating the absolute difference in proportion of subjects achieving a SLEDAI-2K SRI-4 response and who do not meet treatment failure criteria (targeting SRI-4 Primary estimand) in an unblinded fashion by the unblinded DMC.

At the time of the interim analysis, the DMC will make a nonbinding recommendation to either (1) continue the study without modification or (2) terminate the study because of lack of efficacy.

The interim analysis for futility will be a two-step process consisting of the following:

- Step 1: The DMC will assess whether the proportion of subjects achieving SRI-4 composite response at Week 24 in the ustekinumab treated group is ≤ 2% greater than the proportion in the placebo treated group. If the difference is greater than 2%, the DMC will recommend to continue the study without modification. If the difference is ≤ 2%, the DMC will continue to Step #2.
- Step 2: Using the same dataset, the DMC will assess whether the proportion of subjects achieving SRI-4 composite response at Week 52 in the ustekinumab treated group is ≤ 2% greater than the proportion in the placebo treated group. If the difference is greater than 2%, the DMC will recommend to continue the study without modification. If the difference is ≤ 2%, the DMC will recommend to terminate the study.

The decision to use a cutoff of 2% is based upon the observed differences in proportion of SRI-4 composite responders at Week 24 in the completed Phase 2 study (CNTO1275SLE2001), estimated clinically significant differences in response rate as well as minimizing the risk to incorrectly claim futility. Operating characteristics of the futility analysis are shown in Table 2 below:

Table 2: Operating Characteristics of Interim Analysis for Futility			
Assume True Delta in Population	Threshold for Decision Rule[a]	Probability of Claiming Futility	Power[b]
0	2%	50.1%	4.5%
5	2%	30.1%	19.4%
10	2%	12.3%	51.2%
15	2%	4.9%	82.6%
20	2%	1.3%	96.0%
25	2%	0.1%	99.9%
30	2%	0.0%	100.0%
0	4%	65.1%	3.5%
5	4%	39.9%	17.1%
10	4%	20.6%	47.4%
15	4%	7.9%	80.4%
20	4%	2.8%	94.7%
25	4%	0.2%	99.8%
30	4%	0.1%	99.8%

Futility analysis performed 24 weeks after 50% of the planned subjects have been randomized.
The futility analysis probabilities are based upon observing the cutoff at both Weeks 24 and 52 for the sample.
Delta represents the Difference in Proportions between ustekinumab and placebo (ustekinumab minus placebo)
[a] Observed delta to claim futility (i.e., if observed Week 24 delta is < threshold and observed Week 52 delta is < the threshold)
[b] Power at Week 52 primary DBL for the study given that the futility analysis is performed

Although the DMC will make a recommendation to the Sponsor, the Sponsor will make the final decision of the action taken. The use of an independent, external DMC and Statistical Support Group as well as the communication plan discussed throughout the DMC Charter result in limited interactions of the independent DMC and the study team. Additionally, unblinding information used for reviews is sequestered from the study team. This should ensure protection of study integrity. The fact that the DMC is only privy to the difference in proportions of responders between the treatment groups during the interim analysis for futility and not the individual or group level response rates is an additional measure in place to ensure study integrity.

If the recommendation from the DMC is to terminate the study, initially, the Sponsor Committee would be unblinded to confirm that the futility criteria were met. If additional analysis were to be performed to support continuing the study unmodified, those involved in the unblinding would not be involved in the conduct of the study and the list of personnel would be documented prior to any analysis. Further details for the Interim Analysis are included in the DMC Charter and DMC SAP.

3.2. Data Monitoring Committee

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

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

Periodic safety reviews will occur as outlined in the DMC Charter, initiating when the 30th subject reaches their Week 12 visit and then occurring approximately 6-monthly until the last meeting is within 6 months of the Week 52 database lock. The Interim Analysis described in Section 3.1 will coincide with the 3rd DMC scheduled meeting.

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

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

4. SUBJECT INFORMATION

The number of subjects in each analysis set will be summarized and listed by treatment group, and overall. In addition, the distribution of subjects by region, and country will be presented.

4.1. Demographics and Baseline Characteristics

Table 3 presents a list of the demographic variables and disease characteristics that will be summarized by treatment group and overall for the randomized analysis set. Prior and concomitant medications used at baseline will be listed.

Age will be calculated as (date of informed consent – date of birth + 1) / 365.25 in units of years.

BMI will be calculated as weight/height^2 with units of kg/m^2.

Table 3: Demographic Variables and Disease Characteristics at Baseline

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m^2)	
SLEDAI-2K score (0-105)	
PGA score (0-3)	
SLE Duration (years)	
Number of Active Joints (0-62)	
Number of Tender Joints (0-64)	
Number of Swollen Joints (0-62)	
CLASI Activity Score (0-70)	
Categorical Variables	**Summary Type**
Age ([16-25 years, 26-50 years, 51-64 years, and ≥65 years])	Frequency distribution with the number and percentage of subjects in each category.
Sex (male, female)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
BMI ([normal ≤25 kg/m^2, overweight 25-<30 kg/m^2, obese ≥30 kg/m^2])	
Proportion with Lupus Nephritis Present (%)	
Proportion with Anti-dsDNA Antibody Positivity (%)	
Proportion with Anti-Smith Antibody Positivity (%)	
Proportion with Anti-Nuclear Antibody Positivity (%)	
Proportion with Low Complement C3 (%)	
Proportion with Low Complement C4 (%)	
Proportion with at least 1 BILAG A Score (%)	
Proportion with at least 2 BILAG B Scores (%)	
Proportion with at least 1 BILAG A Score or at least 2 BILAG B Scores (%)	

[a]If multiple race categories are indicated, the Race is recorded as 'Multiple'

Additionally, the proportion of subjects receiving selected concomitant medications at baseline (e.g. glucocorticoids, anti-malarials, mycophenolate mofetil [MMF]/Mycophenolic Acid [MPA], azathioprine [AZA]/6-mercaptopurine [6-MP], methotrexate [MTX]) and average dose of concomitant medication(s) will be summarized by treatment group.

4.2. Disposition Information

Disposition information will be based upon the randomized analysis set.

The number of subjects in the following disposition categories will be summarized by treatment group:

- Subjects randomized
- Subjects treated
- Subjects completing the study
- Subjects who discontinued study agent and reasons for discontinuation

- Subjects who terminated study prematurely and reasons for termination
- Subjects who met treatment failure criteria and reason

4.3. Treatment Compliance

During the double-blinded study period, study agent will be administered as an IV (initial dose) and SC injection by authorized and qualified staff personnel and the details of each administration will be recorded in the electronic case report form (eCRF) including date, start and stop times for infusion, and start time for injection. Compliance with the treatment agent will be controlled by the study site personnel.

Study agent compliance will be summarized descriptively. Compliance to randomized treatment versus actual treatment will be presented in a summary table. Additionally, subjects may be summarized by the study agent lot(s) received.

4.4. Extent of Exposure

The number of subjects exposed to study agent, the number of administrations of study agent by type of administration (IV and SC), and cumulative dose (IV and SC) of study agent will be summarized by randomized treatment group.

4.5. Protocol Deviations

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

- Subjects who entered but did not satisfy entry criteria
- Subjects who received the wrong treatment or incorrect dose
- Subjects who developed withdrawal criteria but were not withdrawn
- Subjects who received a disallowed concomitant medication
- Other deviations (e.g. missed visits for reasons other than AEs, unblinding error, actions deemed as major deviations by the study team)

4.6. Prior and Concomitant Medications

Background medication use for active SLE will be summarized by treatment group. New medication, prohibited medication or medication dose increased from baseline dose for SLE will be listed and the dose of that medication will be summarized.

Prior and concomitant medications will be coded according to the World Health Organization (WHO) encoding dictionary, and the number and percent of subjects receiving each medication in each treatment group will be summarized by Level 3 Anatomical Therapeutic Chemical Classification (ATC) code (first four numbers in the code).

Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study agent. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study agent, including those that started before and continue after the first dose (partial or complete) of study agent.

4.7. COVID-19 Related Summaries

Subject disposition as related to COVID-19 will be summarized by treatment group. This includes the following COVID-19 related disposition events:

- Termination of study due to COVID-19 (pandemic and/or disease) and reason
- Discontinuation of study agent due to COVID-19 and reason
- Death related to COVID-19

Subjects discontinuing treatment or terminating study participation due to COVID-19 and reason(s) will be listed.

Assessment of study compliance as related to COVID-19 will be summarized, including number of missed visits, and number of remote visits conducted. Subjects whose visit compliance was impacted by COVID-19 will be listed.

Depending on the extent of the COVID-19 impact on the study, subgroup analyses may be defined on a study level to evaluate the impact (e.g., different periods of the pandemic: pre-COVID-19, during COVID-19, post-COVID-19)

Subjects receiving concomitant medications related to COVID-19 infection will be listed.

Major protocol deviations as related to COVID-19 will be summarized and listed.

Study agent modifications due to COVID-19 will be summarized and listed.

5. EFFICACY

5.1. Analysis Specifications

5.1.1. Level of Significance

Unless otherwise stated, the statistical significance is set to a 2-sided α-level of 0.05 as per protocol. Where appropriate, 95% confidence intervals will be provided.

Unless otherwise stated, efficacy analyses will be performed on the FAS subjects who should have had a given visit based upon their latest scheduled study visit and the trial termination date of 26th June 2020 (See Section 2.3.2.1).

5.1.2. Multiplicity Adjustment for Testing Procedures

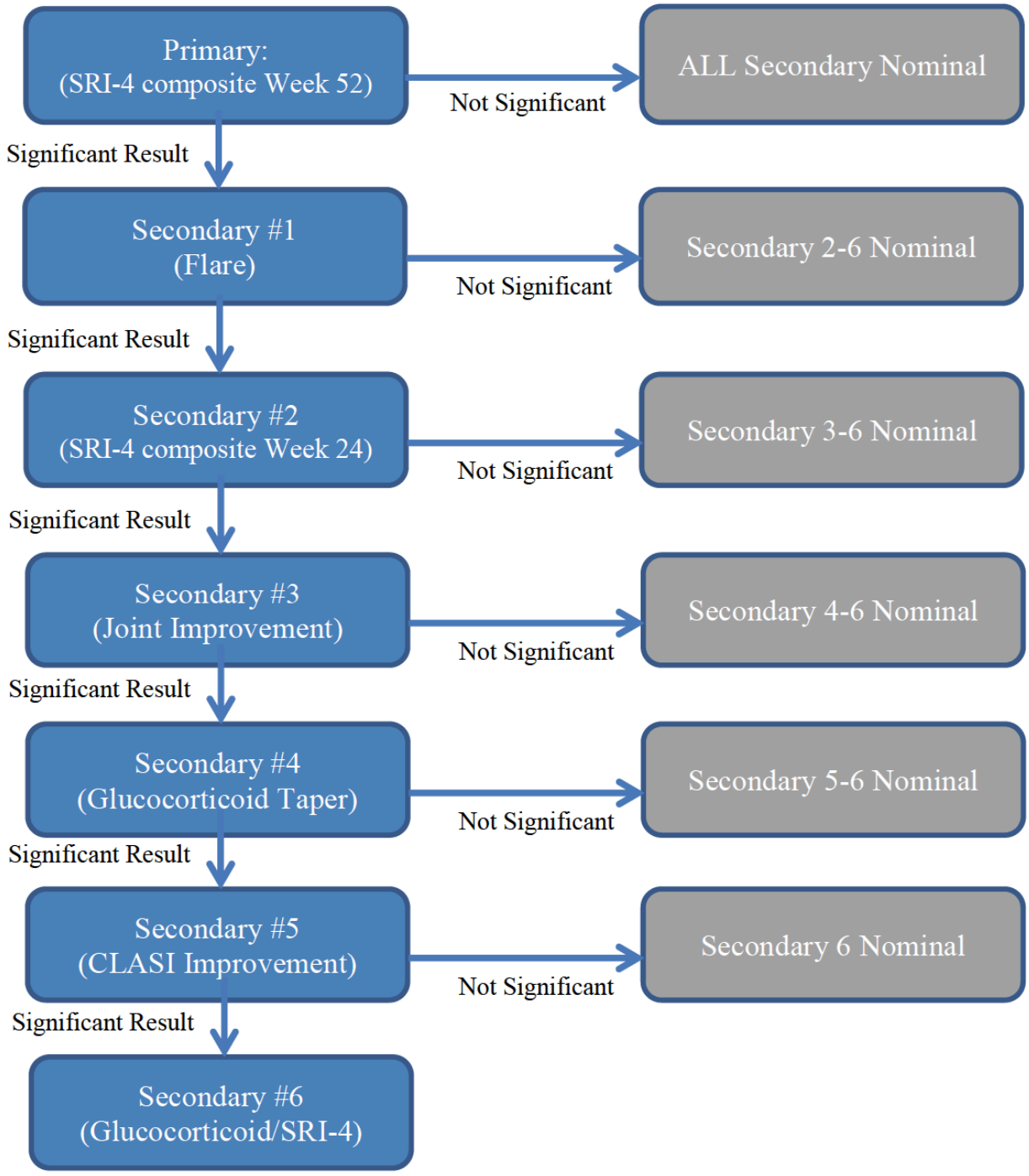
The primary endpoint of this study is the proportion of subjects achieving a SRI-4 composite response at Week 52.

There are 6 major secondary endpoints in this study:

1. Time to first flare based on the proportion of subjects with a flare occurring at any time after the baseline visit through Week 52, with flare defined as either 1 or more new BILAG A or 2 or more new BILAG B scores.
2. The proportion of subjects with a SRI-4 composite response at Week 24
3. The proportion of subjects achieving at least a 50% improvement in the number of joints with pain and signs of inflammation (active joints) at Week 52 in subjects with at least 4 affected joints at baseline
4. The proportion of subjects who achieve reduction in glucocorticoid dose by Week 40 and sustain that reduction through Week 52 in those subjects receiving glucocorticoids at baseline (See Section 5.3.1.6 for definitions of reduction of glucocorticoid dose and sustained reduction of glucocorticoid dose.)
5. The proportion of subjects achieving at least a 50% improvement in the CLASI Activity Score at Week 52 in subjects with a CLASI Activity Score of 4 or greater at baseline
6. The proportion of subjects who (1) achieved reduction in glucocorticoid dose by Week 40 and sustained that reduction through Week 52 and (2) achieved a SRI-4 composite response at Week 52 (Subjects must meet both criteria #1 and #2) in those subjects receiving glucocorticoids at baseline

A serial gatekeeping (fixed sequence) approach will be applied to adjust for multiplicity and to strongly control type I error across the primary and major secondary endpoints. First, the primary endpoint will be tested to compare ustekinumab with the placebo group at a 2-sided α-level of 0.05. If the test is significant, the hypotheses of the major secondary endpoints will be tested in a fixed sequence at the 2-sided α-level of 0.05 as follows (Figure 2). If a given comparison is not significant at the 2-sided α level of 0.05, the remaining treatment group comparisons will be considered supportive analysis.

Figure 2: Primary and Secondary Testing Hierarchy



5.1.3. Data Handling Rules

No imputation will be performed for missing baseline values.

If an investigational site is closed for non-compliance with study processes and procedures as outline in the protocol and training materials, the following actions will be taken regarding all subject data collected at the site;

- All efficacy data collected will be considered un-evaluable and will be excluded from any efficacy analysis. No imputation for the missing subject data will be performed.
- All safety and PK data collected will be included in safety and PK analyses (except those PK analyses regarding efficacy).

Primary Endpoint:

- For the primary endpoint, subjects meeting treatment failure criteria will be imputed as non-responders from the point of treatment failure onward. Missing data will be imputed as non-response. Sensitivity analyses will be performed using observed data regardless of whether the subject met treatment failure criteria.

Binary major secondary endpoints:

- Analyses will be similar to the main analysis of the primary endpoint: subjects meeting treatment failure criteria will be imputed as non-responders from the point of treatment failure onward. Missing data will be imputed as non-response.

Continuous endpoints, if applicable:

- Observations after meeting treatment failure criteria will be set to missing for subjects who met the criteria. No imputation will be performed for missing post baseline continuous values; the statistical model (i.e., MMRM) will adjust for missing post baseline data.

For all other binary endpoints, analyses will be similar to the main analysis of the primary endpoint: subjects meeting treatment failure criteria will be imputed as non-responders from the point of treatment failure onward. Missing data will be imputed as non-response.

In addition, selected data may also be reported using observed data without applying these data handling rules.

5.1.3.1. Treatment Failure

Treatment failure criteria is applied during the double-blind portion of the study.

Treatment Failure Criteria: Subjects who have 1 or more of the following events (due to increased SLE disease activity) will be defined as treatment failures from the point of the occurrence of the event onward:

*Note: Where replacement of a medication (i.e. dose equivalent is equal or less than current dose) is permitted, the reason for replacement should not be due to SLE worsening. If the replacement is due to SLE worsening, the subject may be classified as a treatment failure.

Antimalarial Medications

- Between the Week 12 and the Week 52 visit either; (a) exceeding the baseline dose of antimalarial treatment, or (b) initiation of a new (not present at randomization) antimalarial treatment and this antimalarial does not replace a current antimalarial (i.e. dose equivalent is equal or less than current dose)
- Addition of a new antimalarial to the existing treatment regimen (not present at randomization) before Week 12 and the subject still was receiving that antimalarial after Week 12 and this antimalarial does not replace a current antimalarial (i.e. dose equivalent is equal or less than current dose)

Oral Glucocorticoids for SLE Disease Activity

- Between the Week 12 and the Week 52 visit either; (a) exceeding the baseline average daily dose of oral glucocorticoid treatment, or (b) initiation of a new (not present at randomization) oral glucocorticoid treatment and this glucocorticoid does not replace a current glucocorticoid (i.e. dose equivalent is equal or less than current dose)
- Addition of a new oral glucocorticoid treatment to the existing treatment regimen (not present at randomization) before Week 12 and the subject still was receiving that oral glucocorticoid after Week 12 and this glucocorticoid does not replace a current glucocorticoid (i.e. dose equivalent is equal or less than current dose)

Non-biologic Immunomodulators (Mycophenolate mofetil [MMF], Mycophenolic acid [MPA], Azathioprine [AZA], 6-mercaptopurine [6-MP], Methotrexate [MTX])

- Between the Week 12 and the Week 52 visit either; (a) exceeding the baseline dose of immunomodulator treatment, or (b) initiation of a new (not present at randomization) immunomodulator treatment and this immunomodulator does not replace a current immunomodulator (i.e. dose equivalent is equal or less than current dose) of similar mechanism of action (e.g. MMF substitution for MPA or vice versa, AZA substitution for 6-MP or vice versa, MTX oral can replace MTX subcutaneous (or intramuscular) or MTX subcutaneous (or intramuscular) can replace MTX oral)
- Addition of a new immunomodulator treatment to the existing treatment regimen (not present at randomization) before Week 12 and the subject still was receiving that immunomodulator after Week 12 and this immunomodulator does not replace a current immunomodulator (i.e. dose equivalent is equal or less than current dose) of similar mechanism of action (e.g. MMF substitution for MPA or vice versa, AZA substitution for 6-MP or vice versa)

Prohibited medications

- Between randomization and Week 52, initiation of any protocol prohibited medication with the following exceptions:
  - If clinically necessary, a total of 1 or 2 IA injections may be permitted for SLE up to the Week 12 visit and will be recorded as a medical procedure and as concomitant medication
  - Up to the Week 12 visit, short-term (≤2 weeks) epidural, IV, IM, intrabursal, or intralesional glucocorticoid for the treatment of conditions other than SLE is permitted and should be limited to situations where, in the opinion of the Investigator, there are no adequate alternatives. However, intravenous glucocorticoid exceeding 625 mg prednisone equivalent/day for 2 or more days are not permitted at any time

Discontinuation:

- Subjects who discontinue study agent for any reason prior to Week 52 will be classified as a treatment failure from the point of discontinuation forward

Depending on the estimand of interest, different data handling rules will be applied to Treatment Failures.

Subjects who met treatment failure criteria and reason for meeting criteria will be listed.

Periodic review for subjects meeting the above treatment failure criteria is performed by the blinded sponsor medical monitors. The periodic review process consists of (1) applying programmatic definitions of treatment failure based upon the above criteria to the collected data to generate listings of subject meeting treatment failure criteria and (2) medical monitor in-depth assessment of clinical data including concomitant medications, medical history, laboratory assessments, and potentially other pertinent information to confirm the treatment failure criteria met and (3) maintaining results of the reviews within a tracking document. All subjects meeting treatment failure criteria will be reviewed in a blinded manner. Within the programmed dataset(s), there will exist variables for the programmed treatment failure criteria met, the confirmed treatment failure criteria met after medical review, as well as a detailed summary reason for any differences between the programmed and clinically reviewed treatment failure criteria. The medically reviewed and confirmed treatment failure variables will serve as the basis for all analyses where treatment failure rules are in effect.

Subjects who met treatment failure criteria, reason for meeting criteria, confirmed treatment failure criteria, and detailed summary of reason for any differences between the programmed and clinically reviewed treatment failure criteria will be listed.

5.2. Primary Efficacy Endpoint(s)

The primary efficacy endpoint is the proportion of SRI-4 composite responders at Week 52.

5.2.1. Definition

SLEDAI-2K SRI-4 response is defined as ≥4-point reduction from baseline in SLEDAI-2K score (see Section 5.3.1.3), no new BILAG A and no more than 1 new BILAG B domain score, and no worsening from baseline in the Physician's Global Assessment (PGA) of Disease Activity (<10% worsening from baseline).[4] For the primary endpoint analysis, SRI-4 composite response is the proportion of subjects who achieve a SLEDAI-2K SRI-4 response at Week 52 and do not meet treatment failure criteria prior to Week 52.

5.2.2. Estimands

Primary Endpoint Analysis:

The **Primary Estimand** will be targeted for the primary endpoint. The Primary Estimand for the primary endpoint is defined by the following:

- Population: Subjects in the FAS with active SLE who have not adequately responded to one or more standard-of-care treatments.
- Variable: Proportion of SRI-4 composite response at Week 52
- Intercurrent event: The following intercurrent events are to be taken into account:
    1. If a subject takes medication that meets treatment failure criteria or discontinues treatment (see treatment failure rules for details), assume non-response from the point of treatment failure onward.
- Population-level summary: Difference in the proportion of subjects achieving SRI-4 composite response at Week 52 between the ustekinumab and placebo treatment groups.

Supplementary Estimands:

A supplementary **Treatment Policy (de Facto) Estimand** is also considered. The Treatment Policy (de Facto) Estimand for the primary endpoint is defined by the following:

- Population: Subjects in the FAS with active SLE who have not adequately responded to one or more standard-of-care treatments.
- Variable: Proportion of SRI-4 composite response at Week 52
- Intercurrent event: The occurrence of an intercurrent event is irrelevant. All observed values will be used regardless of occurrence of an intercurrent event.
- Population-level summary: Difference in the proportion of subjects achieving SRI-4 composite response at Week 52 between the ustekinumab and placebo treatment groups.

5.2.3. Analysis Methods: Primary Endpoint

In general, the statistical software SAS® will be used for all data analysis.

Analysis of the primary efficacy endpoint (SRI-4 composite response at Week 52) will utilize the Primary Estimand and be based upon the FAS excluding those subjects whose projected Week 52 visit occurred after study termination (see Section 2.3.2.1).

Sensitivity analyses will be performed and include an analysis based upon the entire FAS (See Section 5.2.3.2).

The following outlines the analysis method:

As per the primary estimand, if a subject takes medication that meets treatment failure criteria or discontinues treatment (see treatment failure rules in Section 5.1.3.1 for details), assume non-response from the point of treatment failure or treatment discontinuation onward. Additionally, if a subject is lost to follow-up (i.e. missing data) assume non-response.

Logistic regression, adjusting for baseline stratification factors, region and baseline SLEDAI-2K score (continuous variable), will be used to analyze the primary endpoint. The logistic regression model will include treatment group, region, stratification factors as described in Section 1.5 (race, presence of lupus nephritis at baseline, composite of baseline SLE medications [high/low] and clinical SLEDAI score [<10, ≥10] at baseline) and baseline SLEDAI-2K score (continuous variable). The baseline SLEDAI-2K score will be defined as the closest non-missing measurement taken prior to the Week 0 infusion.

The metric utilized for comparison across treatment groups will be the odds ratio. The odds ratio associated 95% Wald, asymptotic method confidence intervals[1] and the statistical significance of the difference in treatment effect will be reported. In addition to the odds ratios and confidence interval, the difference in proportions and associated confidence interval[1] will be provided as supplementary results.

5.2.3.1. Subgroup Analyses

Subgroup analysis of the primary endpoint based on region will be performed. This is due to potential regional differences in efficacy, safety, treatment practices and higher placebo response rates in certain regions. Subgroup analysis of the primary endpoint by other selected baseline characteristics may be presented when the number of subjects in the subset permits (at least 15 subjects for each treatment group within a subset):

1. Subgroups defined by demographics
    a. Region (APAC, LA, EEU, Africa, NA, WEU)
    b. Race (White, Black, Asian, All other categories)
    c. Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
    d. Age (16-25, 26-55, Over 55)
    e. Body Weight (≤ 55 kg, > 55 and ≤ 85 kg, > 85 kg)

f. BMI (Normal [< 25 kg/m^2], Overweight [≥ 25 to < 30 kg/m^2], Obese [≥ 30 kg/m^2])

g. Sex (Male, Female)

h. Subjects age at SLE diagnosis (≤ 21 Years, > 21 Years)

2. Subgroups defined by baseline characteristics

a. Combined factor of baseline SLE Medication (High, Medium) and SLEDAI-2K score (≥ 10, <10)

b. SLEDAI-2K Score (< Median, ≥ Median)

c. PGA Score (< Median, ≥ Median)

d. Presence of lupus nephritis at baseline (Y, N)

e. Urine Protein/Creatinine Ratio at baseline (< Median, ≥ Median)

f. Serologic status individually and collectively for anti-dsDNA, C3 and C4

i. dsDNA (positive, negative)

ii. Complement C3, C4 (normal, abnormal)

g. SLE medication use at baseline

For subgroup analyses, odds ratios and corresponding 95% confidence intervals will be presented graphically. Additionally, nominal p-values for the comparison across treatment groups for the subgroups as well as for the interaction between treatment groups will be presented.

5.2.3.2. Sensitivity Analyses

Termination of the study due to futility resulted in a significant change to the planned sensitivity analyses in this section. Please see SAP Amendment #1, dated January 8th, 2020 for originally planned analyses.

Sensitivity Analysis 1 (Treatment Policy Estimand): In order to assess both components of the primary endpoint (1) subjects remaining in the study at week 52, on treatment, and not meeting treatment failure criteria and then in that subset (2) those achieving a SRI-4 response at Week 52 the following analyses will be performed:

- Analysis 1A: To assess component #1 of the primary endpoint we will include a summary (number and percentage of subjects in each treatment group) of subjects who remain in the study at Week 52, on treatment and do not meet treatment failure criteria.
- Analysis 1B: To address component #2 of the primary endpoint, subjects who have an observed SRI-4 value at Week 52 will be included.

Sensitivity Analysis 2 (Primary Estimand): The primary endpoint will be analyzed utilizing the FAS. In this analysis, subjects whose projected Week 52 visit occurs after study termination will **not** be excluded from the analysis set.

Sensitivity Analysis 3 (Primary Estimand): In the event that mis-stratification occurs in greater than 10% of subjects, the primary endpoint will be analyzed using stratification factors taken from the electronic data capture (EDC) system instead of the IWRS system.

See Section 5.2.4 for further details on these analyses.

Table 4 below shows the assumptions of each considered analysis for the primary efficacy endpoint, all applied to the full analysis set defined in Section 2.3.2:

Table 4: Analysis Types and Assumptions

Analysis Type	Estimand	Analysis Method	Assumption
Primary Analysis	Primary (FAS excluding Week 52 projected after termination)	Non-responder imputation for data after intercurrent event and missing data. Logistic regression.	Missing not at Random: Missing data and intercurrent event indicates lack of response
Sensitivity Analysis #1A (component 1)	Treatment Policy	No imputation, summary of data	No assumptions
Sensitivity Analysis #1B (component 2)	Treatment Policy	No imputation for missing data, logistic regression	Missing Completely at Random: completers are representative of non-completers
Sensitivity Analysis #2	Primary (FAS)	Non-responder imputation for data after intercurrent event and missing data. Logistic regression.	Missing not at Random: Missing data and intercurrent event indicates lack of response
Sensitivity Analysis #3	Primary (FAS excluding Week 52 projected after termination)	Non-responder imputation for data after intercurrent event and missing data. Logistic regression.	Missing not at Random: Missing data and intercurrent event indicates lack of response

5.2.4. Analysis Methods: Sensitivity Analyses

5.2.4.1. Component Analysis (Sensitivity Analysis 1)

Analysis 1A: The primary endpoint will be summarized (number and percentage in each treatment group) utilizing the Treatment Policy (de Facto) Estimand.

Analysis 1B: The primary endpoint will be analyzed utilizing the Treatment Policy (de Facto) Estimand. Logistic regression similar to the primary analysis as outlined in Section 5.2.3 will be performed.

5.2.4.2. Primary Endpoint using the Full Analysis Set (Sensitivity Analysis 2)

The primary endpoint will be analyzed using the entire FAS where subjects whose projected Week 52 visit occurs after study termination will be **included** in the analysis set. Therefore, all subjects who were randomized and received at least 1 dose (partial or complete, IV or SC) of study agent will be included in the analysis.

5.2.4.3. Stratification Analysis (Sensitivity Analysis 3)

The primary endpoint will be analyzed as outlined in Section 5.2.3 using logistic regression, adjusting for baseline stratification factors, region and baseline SLEDAI-2K score (continuous variable). Based upon the ITT principle, the primary analysis uses the IWRS data for categorical stratification factors. For this sensitivity analysis, the categorical stratification factors (race, presence of lupus nephritis at baseline, composite of baseline SLE medications [high/low] and clinical SLEDAI score [<10, ≥10] at baseline) will be taken from the electronic data capture (EDC) system instead of the 'as stratified' data within the IWRS system.

5.3. Major Secondary Endpoints

The secondary endpoints are the following:

1. Time to first flare based on the proportion of subjects with a flare occurring at any time after the baseline visit through Week 52, with flare defined as either 1 or more new BILAG A or 2 or more new BILAG B scores
2. The proportion of subjects with a SRI-4 composite response at Week 24
3. The proportion of subjects achieving at least a 50% improvement in the number of joints with pain and signs of inflammation (active joints) at Week 52 in subjects with at least 4 affected joints at baseline
4. The proportion of subjects receiving glucocorticoids at baseline who achieve reduction in glucocorticoid dose by Week 40 and sustain that reduction through Week 52 (See Section 5.3.1.6 for definitions of reduction of glucocorticoid dose and sustained reduction of glucocorticoid dose.)
5. The proportion of subjects achieving at least a 50% improvement in the CLASI Activity Score at Week 52 in subjects with a CLASI Activity Score of 4 or greater at baseline
6. The proportion of subjects receiving glucocorticoids at baseline who achieve reduction in glucocorticoid dose by Week 40, sustain that reduction through Week 52 and achieve a SRI-4 composite response at Week 52 (Subjects must meet all criteria)

5.3.1. Definition

5.3.1.1. British Isles Lupus Assessment Group (BILAG)

The British Isles Lupus Assessment Group (BILAG)[5,6] index scores subjects based on the need for alterations or intensification of therapy. The assessing physician will evaluate 97 items divided into 9 organ system domains. The physician considers presence of each item in the past 4 weeks and answers 0=not present, 1=improving, 2=same, 3=worse, or 4=new. Each organ/system domain is classified programmatically or by data reviewers as BILAG A, B, C, D, or E based upon criteria specific to the domain.[6] The BILAG index was designed to give practicing physicians a tool to help in decision-making based on amount of activity in each organ/system. The baseline measurement for the BILAG is defined as the closest measurement taken during the study and prior to administration of study agent at Week 0.

Adjudicated Flare: Adjudication for a flare is performed by a blinded adjudication committee consisting of clinicians with expertise in lupus disease features and clinical assessment tools. The adjudication process consists of (1) applying programmatic definitions of BILAG and modified SELENA Flare Index (mSFI) flares to the eCRF collected data to generate a listing of subjects with flares and (2) three independent and experienced blinded reviewers will then perform an in-depth assessment of clinical data including BILAG, SLEDAI-2K, PGA, modified SELENA flare index, CLASI, joint count assessments, concomitant medications, medical history, laboratory assessments, and potentially other pertinent information to confirm or adjudicate the flare. In the event that the primary reviewers disagree on the flare status the final determination of true vs. false flare for each case will be based on majority (2 out of 3 evaluators) vote. In rare instances regarding complex cases, additional external subject matter expert(s) may be consulted to provide an evaluation of the flare, and consensus may be reached by committee after a discussion amongst the reviewers and external experts.

All flares will be adjudicated regardless of whether it is the subject's first flare or an additional flare occurring in either the same or a different organ system. Within the programmed dataset, there will exist variables for the programmed flare, adjudicated flare, as well as a detailed summary of the reason for adjudication. The adjudicated flare variables will serve as the basis for the flare endpoints. Details of the flare adjudication process will also be provided in a separate adjudication manual.

Note: Flares that are determined to be due to COVID-19 will be excluded from flare analyses (i.e. the subject will not be censored for a COVID-19 related flare and subject would not have been considered to have had a flare). The reason(s) for exclusion will be discussed. Any non COVID-19 related flare in the future would be included. Analyses where these such flares are included may be conducted. Note that adjudication of COVID-19 related flares is part of the formal adjudication process.

BILAG Flare: Defined as at least 1 new BILAG A or at least 2 new BILAG B scores meeting at least one of the following criteria:

- Not present at baseline
- The occurrence of a new/worse manifestation in a different component of a domain that is already present
- At least 1 A or 2 B scores in a domain which improves to B/C/D for at least 2 sequential study visits followed by new/worse disease activity

Refer to the Flare Charter for more detailed definitions and programming rules.

Time to First Flare: Time to first flare is defined as the time (in days) after baseline when a given subject experiences his or her first flare. Time to first flare is calculated as the date of the first flare minus the date of randomization day + 1.

5.3.1.2. SRI-4 Composite Response

See Section 5.2.1 for definition

5.3.1.3. Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)

The SLE disease activity index 2000 (SLEDAI-2K/SLEDAI-2K RI-50) 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 at the time of the visit or in the previous 30 days; the index is weighted according to the feature. Features are scored by the assessing physician if present at the time of the visit 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.[7] The baseline measurement for each of the 24 features of the SLEDAI-2K is defined as the closest measurement taken prior to the initiation of the Week 0 study agent administration. The baseline SLEDAI-2K score will be derived from these 24 features.

The SLEDAI-2K has been adapted and developed into the SLEDAI-2K RI-50,[8] a measure that can document partial improvement in the 24 disease features among SLEDAI-2K assessments. A threshold of 50% improvement was judged to reflect clinically significant improvement and is scored as half the weight for the feature. "When a descriptor is recorded as present at the initial visit, 1 of 3 situations can follow: (1) the descriptor achieves complete remission at follow-up, in which case the score would be "0"; (2) the descriptor does not achieve a minimum of 50% improvement at follow-up, in which case the score would be identical to its corresponding SLEDAI-2K value; or (3) the descriptor improves by ≥50% (according to the SLEDAI-2K RI-50 definition) but has not achieved complete remission, in which case the score is evaluated as one-half the score that would be assigned for SLEDAI-2K." The SLEDAI-2K RI-50 score is the sum of the 24 scored items, which ranges from 0 to 105.

For this study, the developer of the SLEDAI-2K/SLEDAI-2K RI-50 instrument has modified scoring disease activity on S2K RI-50 based solely on physician encounter at the time of the study visit for the following 8 items: Visual disturbance, Cranial nerve disorder, CVA, Vasculitis, Arthritis, Myositis, Rash and Alopecia. This was to ensure reliability of the disease activity assessment by the investigators and reduce patient self-reporting bias. Unless otherwise specified, all references to the SLEDAI-2K within this SAP refer to this modified version.

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. At baseline, the features assessed in the SLEDAI-2K are used for comparison to the SLEDAI-2K RI-50 [Follow-up] described above.

5.3.1.4. Physicians Global Assessment (PGA) of Disease Activity

The Physician's Global Assessment of Disease Activity[3] independent of subjects' assessment is recorded on a 10-cm visual analogue scale (VAS) with responses ranging from 0-3, and verbal anchors "No Lupus Activity" (0) on the far-left side of the scale and "Extremely Active Lupus" (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.

5.3.1.5. Joints with Pain and Signs of Inflammation

Joints with 'pain and signs of inflammation' will be classified as 'active' and be defined as those joints which are tender (i.e. subject reports pain as assessor applies pressure) on examination and exhibit at least one sign of inflammation (e.g. edema of effusion to be considered swollen) on physical examination as determined by the joint assessor.

Assessment of tender, swollen, and both tender and swollen joints will be performed by an adequately trained joint assessor at all visits indicated in the protocol. Joint counts will be assessed using a 64 tender and 62 swollen joint count in accordance with the SLEDAI-2K RI-50 electronic case report form (eCRF), which includes a homunculus depicting the bilateral temporomandibular, sternoclavicular, shoulder, elbow, wrist, metacarpophalangeal, hand proximal interphalangeal, hand distal interphalangeal, hip (only tenderness assessed), knee, ankle, metatarsophalangeal, and foot interphalangeal joints. The joint assessor will record the number of tender, swollen, and both tender and swollen joints and then assess whether the joints demonstrating both tenderness and swelling meet the above definition of 'pain and signs of inflammation' and therefore be considered 'active'. The number of active joints will then be entered on the S2K-RI50 eCRF under the arthritis section. A 50% improvement in the number of active joints is defined as a 50% reduction from baseline in the number of active joints for those subjects with active joints at baseline. The analysis of at least 50% improvement will be performed on subjects with at least 4 active joints at baseline (e.g. subjects with 4 or 5 active joints at baseline would show 50% improvement if the number of joints were reduced to 0,1 or 2).

Local intra-articular injections into joints will deem the joints to be imputed as active (having pain and signs of inflammation) from the point of injection thereafter for the purpose of joint count assessments.

5.3.1.6. Glucocorticoid Reduction

For this study, average daily dose for any given day is the average of the last 7 days dosing, including the day of interest. Note that the dosing days do not have to be consecutive. The average is of the last 7 days where the subject was dosed.

For this study, reduction of glucocorticoid dose is defined as:

- A reduction in average daily oral glucocorticoid dose by at least 50% (relative to the baseline dose)

  OR

- Reduction of average daily oral glucocorticoid dose by at least 25% (relative to the baseline dose) so that the average daily dose is reduced to ≤7.5 mg (prednisone or equivalent)

For this study, sustained reduction of glucocorticoid dose is defined as:

Achieving average daily oral glucocorticoid dose reduction (as described above) between Weeks 24 and 40, and sustaining that reduction through Week 52, in those subjects who, at baseline, were receiving oral glucocorticoids. Note that this will be performed in the subset of randomized subjects who were receiving oral glucocorticoids at baseline.

Minor dose adjustments after reducing glucocorticoid dose are permitted and subjects will still be considered to have sustained reduction. These dose adjustments are permitted after the Week 40 visit up to and including the Week 48 visit. Any dose increase after the Week 48 visit would deem the subject as a non-responder for the endpoint from the point of dose increase onward. These dose adjustments include the following:

- An increase in average daily dose to a maximum of 5 mg (averaged across the period of increase) above the dose reduction achieved and the increased dose does not return to or exceed the baseline dose, that meets the above criteria is permitted. Only one increase in average daily dose (maximum of 5 mg average daily dose above dose reduction achieved and the increased dose does not return to or exceed the baseline dose) for a period of no longer than 7 consecutive days is permitted. The subject will not be considered to have achieved sustained reduction in glucocorticoid dose if either of the following conditions occur:
  1. Average daily dose increase continues for longer than 7 consecutive days
  2. Greater than 1 (> 1) distinct episode of average daily dose increase occurs

- Table 5 below provides examples of possible scenarios.

Table 5: Glucocorticoid Dosing (mg) Examples Within Range of Sustaining Reduction

Baseline Dose	Criteria Achieved	Reduced Dose*	Maximum Increase Allowed *	Maximum Adjusted Dose Allowed
20	50% reduction	10.0	5	15.0
17.5	50% reduction	9.0	5	14.0
15	50% reduction	7.5	5	12.5
10	25% reduction to ≤ 7.5 mg	7.5	2	9.5
7.5	25% reduction to ≤ 7.5 mg	6.0	1	7.0
5	25% reduction to ≤ 7.5 mg	4.0	1	5.0

*Note that maximum increases allowed (column 4) are presented in possible dosing increments, as GC doses are available in 1, 2, 2.5 and 5 mg doses. Reduced doses (column 3) are rounded up to the next possible clinical dose.

Note that a subject meeting the allowed dose adjustment criteria must taper back to their Week 40 reduced dose by the end of the dose increase period.

Missing Glucocorticoid Dosing:

Missing glucocorticoid dosing will only be interpolated for the glucocorticoid efficacy analyses (i.e. Major Secondary endpoints #4 and #6 described in Section 5.3), all other analyses (e.g. safety, concomitant medications) will not interpolate missing values.

In general, if a subject or investigator indicates that a dose was skipped (i.e. dose data is not missing, dose of medication was not taken) the dose will be entered as a 0 mg dose.

If glucocorticoid dosing is missing at baseline, no interpolation will be performed.

If a subject has baseline and at least 1 post baseline dose measurement, the following interpolation will be performed:

- Unless otherwise specified, missing dose will be interpolated as the average of (1) the actual dose taken on the last day before the missing value(s) and (2) the actual dose taken on first day after the missing value(s).
- Although the missing dose data will be interpolated, in those analyses where treatment failure rules are in effect, a subject's response status will either be set to non-response (Primary Estimand analyses) or missing (Hypothetical Estimand) from the point of treatment failure onwards.

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

Cutaneous lupus disease activity and severity will be measured by the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI). The CLASI is an instrument to assess the disease activity and damage caused to the skin for cutaneous lupus erythematosus (CLE) patients with or without systemic involvement. The CLASI consists of 2 scores; the first summarizes the activity of the disease while the second is a measure of the damage caused by the disease (CLASI Activity and CLASI Damage scores). Activity is scored by the Investigator based on erythema, scale/hyperkeratosis, mucous membrane involvement, acute hair loss, and non-scarring alopecia. Damage is scored in terms of dyspigmentation and scarring, including scarring alopecia. The scores are calculated by simple addition based on the extent of the symptoms.[9]

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

5.3.2. Analysis Methods: Secondary Endpoints

Analyses for binary secondary endpoints (proportion of response, improvement, reduction) will be based upon the Primary Estimand and utilize the FAS excluding those subjects whose projected Week 52 visit occurred after study termination. (see Section 2.3.2.1)

Supportive analyses will be performed and include an analysis based upon the entire FAS (See Section 5.4). Time to flare analyses will also be based upon the Primary Estimand and FAS excluding those subjects whose projected Week 52 visit occurred after study termination where

loss to follow-up patients will be censored and patients who discontinue study treatment (as described below) or initiate rescue therapy will be considered to have a flare.

- For this study, reasons for discontinuation of study treatment include: (1) adverse event (2) death (3) prohibited medication (4) lack of efficacy (5) loss to follow up (6) non-compliance with study drug (7) physician decision (8) protocol deviation (9) pregnancy (10) study terminated by sponsor (11) withdrawal by parent or guardian (12) withdrawal by subject and (13) other. For the primary time to flare analysis those who discontinue study treatment for the following reasons: (1) adverse event (2) death (3) prohibited medication or (4) lack of efficacy will be considered to have a flare, while subjects who discontinue study treatment for the remaining reasons will not be considered to have a flare and their observed data will be used, unless they initiate rescue therapy.

Note: Flares that are determined to be due to COVID-19 will be excluded from flare analyses (i.e. the subject will not be censored for a COVID-19 related flare and subject would not have been considered to have had a flare). The reason(s) for exclusion will be discussed. Any non COVID-19 related flare in the future would be included. Analyses where these such flares are included may be conducted. Note that adjudication of COVID-19 related flares is part of the formal adjudication process.

The hazard ratio for time to flare data (secondary endpoint #1 in Section 5.3 above) will be estimated using the Cox proportional hazards model, adjusting for baseline SLEDAI-2K score (continuous variable), and its 95% confidence interval will be calculated. The proportional hazards assumption will be verified with appropriate methods (e.g. log-minus-log plots) as part of the analysis. The reported p-values for time to first flare analyses will be derived from a log-rank test and will also be used for multiplicity control. The survival curves will be estimated using Kaplan-Meier estimates.

Binary endpoints (secondary endpoints #2, 3, 4, 5, and 6 in Section 5.3 above) will be analyzed using the same approach as the primary endpoint. Logistic regression, adjusting for baseline stratification factors, region and baseline SLEDAI-2K score (continuous variable) as described in Section 5.2.3 will be used.

In general, point estimates and 95% confidence intervals for comparison between treatment groups will be reported.

5.4. Additional Efficacy Endpoints

As supportive analyses to the primary composite endpoint, the following analyses will be performed on the Primary Estimand (both a FAS analyses excluding those subjects whose projected Week 52 visit occurred after study termination as well as a the entire FAS analyses including those subjects will be performed) as well as the Treatment Policy Estimand. Summary statistics including point estimates, odds ratios and 95% Wald confidence intervals[1] will be reported.

- The proportion of subjects with at least a 4-point improvement compared with baseline in SLEDAI-2K at Week 52
- The proportion of subjects with no worsening from baseline in PGA at Week 52
- The proportion of subjects with no BILAG worsening from baseline (defined as no new BILAG A scores and ≤1 new BILAG B score) at Week 52
- The proportion of subjects with SRI-4, SRI-5, SRI-6, SRI-7, or SRI-8 composite response at Week 52

As supportive analyses to the key secondary endpoints, the following analyses will be performed:

- For the binary key secondary endpoints (#2, 3, 4, 5, and 6 in Section 5.3) a similar analyses as outlined in Section 5.2.3 for the primary endpoint will be performed utilizing the Treatment Policy (de Facto) Estimand.

- For the binary key secondary endpoints (#2, 3, 4, 5, and 6 in Section 5.3) a similar analyses as outlined in Section 5.2.3 for the primary endpoint will be performed utilizing the Primary Estimand and the entire FAS.

As supportive analysis to the time to flare key secondary endpoint, the following 2 analyses will be performed:

1. An analysis using the Treatment Policy Estimand will be performed censoring subjects who are lost-to-follow-up. Patients who continue to be followed in the study, regardless of adherence to study drug or use of ancillary therapies, will be evaluated for flare.
2. An analysis using the modified Treatment Policy Estimand where those who discontinue study treatment for the following reason: (1) adverse event (2) death (3) prohibited medication (4) lack of efficacy (11) withdrawal by parent or guardian (12) withdrawal by subject and (13) other, will be considered to have a flare, while subjects who discontinue study treatment for the remaining reasons will not be considered to have a flare and their observed data will be used, unless they initiate rescue therapy. (See Section 5.3.2 for complete list of possible reasons for discontinuation)

5.4.1. Definition

5.4.1.1. Measures of Improvement in Global Disease Activity

SLEDAI-2K: See Section 5.3.1.3.

SRI-4 Composite Response: SLEDAI-2K SRI-4 response is defined as ≥4-point reduction from baseline in SLEDAI-2K score, no new BILAG A and no more than 1 new BILAG B domain score, and no worsening from baseline in the Physician's Global Assessment (PGA) of Disease Activity (<10% worsening from baseline).[4] SRI-4 composite response is the proportion of subjects who achieve a SLEDAI-2K SRI-4 response and do not meet treatment failure criteria prior to the visit of interest.

SRI-5, SRI-6, SRI-7, SRI-8 Composite Response: Defined as SRI-4 response above however a ≥5-point, ≥6-point, ≥7-point and ≥8-point reduction from baseline in SLEDAI-2K score is required.

Note that for any given SRI composite response, the subset of subjects included in the analysis are those who have a SLEDAI score at baseline greater than or equal to the reduction required for the response (e.g. For the SRI-7 composite response, only subjects with a baseline SLEDAI score ≥ 7 are included in the analysis)

BILAG No Worsening: Defined as no new BILAG A scores and ≤1 new BILAG B score.

No Worsening in PGA: Defined as no significant deterioration (< 1.0 cm increase) in 10 cm visual analogue scale, or < 0.3 point increase on a 0-3 point scale.

5.4.2. Analysis Methods

Unless otherwise specified, the analysis population will be the FAS excluding those subjects whose projected Week 52 visit occurred after study termination as defined in Section 2.3.2. The endpoints will be summarized by treatment groups.

P-values provided for analyses will be nominal.

Binary endpoints (e.g. responder analysis) will be analyzed using the same approach as the primary endpoint. Logistic regression, adjusting for baseline stratification factors, region and baseline SLEDAI-2K score (continuous variable) as described in Section 5.2.3 will be used.

If applicable, continuous endpoints will be analyzed using a Mixed Model for Repeated Measures (MMRM) model to test the difference between treatment groups and adjust for missing data. The models will include baseline SLEDAI score as a covariate and treatment, baseline medication use for SLE (high, medium), race, visit, and an interaction of treatment and visit as fixed effects. The within-subject covariance between visits will be estimated via an unstructured variance-covariance matrix. In case of convergence problems, alternative variance-covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR(1) with separate subject random effect. Comparison of the ustekinumab arm versus placebo will be performed using the appropriate contrast. The normality and equal variance assumptions underlying the MMRM model will be assessed graphically. Residuals from the primary models will be plotted against the predicted values and a QQ plot of the residuals versus the expected quantiles of the standard normal distribution will be presented. If either the equal variance or the normality assumption appears to be grossly violated, other methods including an ANCOVA on ranks model or an appropriate transformation of the primary endpoint might be considered.

The hazard ratio for time to event data will be estimated using the Cox proportional hazards model and its 95% confidence interval will be calculated. The proportional hazards assumption will be verified with appropriate methods (e.g. log-minus-log plots) as part of the analysis. The reported p-values for time to event analyses will be derived from a log-rank test and will also be

used for multiplicity control. The survival curves will be estimated using Kaplan-Meier estimates.

The following Table 6 outlines the efficacy endpoints, types of the analyses, and the data handling rules used through Week 52 for Additional Efficacy Endpoints listed in Section 5.4.

Table 6: Analysis and Data Handling Rules for Supportive Endpoints Listed in Section 5.4

	Endpoint	Estimand	Missing Data Imputation	Type
Measures of Improvement in Global Disease Activity				
1	The proportion of subjects with SRI-4, SRI-5, SRI-6, SRI-7, and SRI-8 composite response at Week 52	Primary (FAS including/excluding Week 52 projected after termination)	Yes – TF considered non-responders. Missing assume non-response.	Binary
		Treatment Policy	No	Binary
2	The proportion of subjects with SRI-4 response at Week 24	Primary (FAS including/excluding Week 24 projected after termination)	Yes – TF considered non-responders. Missing assume non-response.	Binary
		Treatment Policy	No	Binary
3	The proportion of subjects with at least a 4-, 5-, 6-, 7-, or 8-point improvement compared with baseline in SLEDAI-2K at 52	Primary (FAS including/excluding Week 52 projected after termination)	Yes – TF considered non-responders. Missing assume non-response.	Binary
		Treatment Policy	No	Binary
4	The proportion of subjects with no worsening in PGA at Week 52	Primary (FAS including/excluding Week 52 projected after termination)	Yes – TF considered non-responders. Missing assume non-response.	Binary
		Treatment Policy	No	Binary
5	The proportion of subjects with no BILAG worsening compared with baseline at Week 52	Primary (FAS including/excluding Week 52 projected after termination)	Yes – TF considered non-responders. Missing assume non-response.	Binary
		Treatment Policy	No	Binary
Flare				
6	Time to first flare based on the proportion of subjects with a flare occurring at any time after baseline visit through Week 52, with flare defined as either 1 or more new BILAG A or 2 or more BILAG B scores	Treatment Policy	No	Binary
7	Time to first flare based on the proportion of subjects with a flare occurring at any time	Modified	No	Binary

Table 6: Analysis and Data Handling Rules for Supportive Endpoints Listed in Section 5.4				
	Endpoint	**Estimand**	**Missing Data Imputation**	**Type**
	after baseline visit through Week 52, with flare defined as either 1 or more new BILAG A or 2 or more BILAG B scores	Treatment Policy		
Glucocorticoid Sparing (Tapering)				
8	The proportion of subjects receiving glucocorticoids at baseline who achieve reduction in glucocorticoid dose by Week 40 and sustain that reduction through Week 52	Treatment Policy	No	Binary
9	The proportion of subjects receiving glucocorticoids at baseline who achieve reduction in glucocorticoid dose by Week 40, sustain that reduction through Week 52 and achieve SRI-4 composite response at Week 52	Treatment Policy	No	Binary
Musculoskeletal Disease				
10	The proportion of subjects achieving at least a 50% improvement in the number of active joints (defined as joints with pain and signs of inflammation) at Week 52 in subjects with at least 4 active joints at baseline	Treatment Policy	No	Binary
Mucocutaneous Disease				
11	The proportion of subjects who achieve a 50% reduction from baseline in CLASI activity score at Week 52 in those subjects with a baseline CLASI activity score of at least 4	Treatment Policy	No	Binary

5.5. SLEDAI-2K Supportive Analyses

The S2K RI-50 was developed based on the SLEDAI-2K, which in general scores post-baseline disease activity if present at the time of the physician encounter or in the preceding 30 days. However, for this study, the developer of the SLEDAI-2K/SLEDAI-2K RI-50 instrument has modified scoring disease activity on S2K RI-50 based solely on physician encounter at the time of the study visit for the following 8 items: Visual disturbance, Cranial nerve disorder, CVA, Vasculitis, Arthritis, Myositis, Rash and Alopecia. This was to ensure reliability of the disease activity assessment by the investigators and reduce patient self-reporting bias. Unless otherwise specified, all references to the SLEDAI-2K within this SAP refer to this modified version. The remaining 16 items are scored utilizing the 30 day look back. Therefore, post-baseline SLEDAI-2K assessments are based upon this **modified** S2K RI-50. This was to ensure reliability of the disease activity assessment by the investigators and reduce patient self-reporting bias. In addition, we are able to collect more information around partial improvement of disease activity.

On March 30th of 2020, the originally developed SLEDAI-2K utilizing the 30 day look back was implemented in the study and data was to be captured from implementation of the form through the end of the study. This data is in addition to the **modified** S2K/S2K RI-50 data to be collected from study start through the end of the study.

The primary endpoint, SRI-4, as well as all SLEDAI-2K analyses for CNTO1275SLE3001 are based upon the **modified** instrument utilizing the day of study visit for the 8 items reference above. As supportive information, and to demonstrate consistency between utilization of the **modified** instrument and the originally developed S2K RI-50 we will perform various supportive analysis as outlined in this section.

5.5.1. Definition

5.5.1.1. SLEDAI-2K v10Oct2015 (modified SLEDAI-2K/S2K- RI-50)

The SLEDAI-2K v10Oct2015, hereafter referenced as **modified** SLEDAI-2K/S2K RI-50 is the endpoint in both the CNTO1275SLE2001 and CNTO1275SLE3001 studies as defined in Section 5.3.1.3. For 8 of the 24 SLEDAI-2K domains, the post-baseline disease activity score is based solely on physician encounter on the day of study visit. These 8 domains include the Alopecia, Arthritis, Cranial Nerve Disorder, CVA, Myositis, Rash, Vasculitis and Visual Disturbance domains. The first utilization of the **modified** instrument was in the CNTO1275SLE2001 study where it was implemented from study start. The date of that implementation was 10 Oct 2015, therefore the naming convention of this endpoint. All analyses concerning SLEDAI-2K in both the CNTO1275SLE2001 and CNTO1275SLE3001 studies utilize the **modified** SLEDAI-2K data. This includes the SLEDAI-2K component of the primary endpoint, SRI-4.

5.5.1.2. SLEDAI-2K Pre-v2015 (Traditional SLEDAI-2K)

SLEDAI-2K based upon data being obtained from the March 30, 2020 implementation of the originally developed SLEDAI-2K questionnaire and associated eCRF page utilizing the 30 day look back on all SLEDAI-2K components.

However, given the limited data collected for the Traditional SLEDAI-2K due to the study termination, no analyses concerning the Traditional SLEDAI-2K will be performed.

5.5.1.3. SLEDAI-2K Recode

SLEDAI-2K based upon utilizing BILAG to recode the 8 domains (Alopecia, Arthritis, Cranial Nerve Disorder, CVA, Myositis, Rash, Vasculitis and Visual Disturbance) where the disease activity score was based upon physician encounter on the day of study visit. For the other 16 SLEDAI domains, the SLEDAI-2K v10Oct2015 data as collected is utilized.

The following steps were taken in order to re-code the SLEDAI-2K v10Oct2015 into the SLEDAI-2K Recode based upon a BILAG re-coding algorithm:

1. Define mapping of BILAG components to SLEDAI-2K Domains as follows:

SLEDAI Domain	BILAG Components Utilized in Mapping

Alopecia	Alopecia severe, Alopecia mild
Arthritis	Arthritis severe, Arthritis moderate
Cranial Nerve Disorder	Cranial neuropathy
CVA	Cerebrovascular disease
Myositis	Myositis severe, Myositis mild
Rash	Skin eruption severe, Skin eruption mild, Panniculitis/bullous lupus severe, Panniculitis/bullous lupus mild, Peri-ungal erythema/chilblains
Vasculitis	Major cutaneous vasculitis/thrombosis, Digital infarcts or nodular vasculitis, Splinter haemorrhages, Cerebral vasculitis, Pulmonary haemorrhage/vasculitis, Aortitis, Coronary vasculitis, Lupus enteritis/colitis
Visual Disturbance	Severe keratitis, Posterior uveitis/retinal vasculitis severe, Retinal/choroidal vaso-occlusive disease, Isolated cotton-wool spots, Optic neuritis, Anterior ischaemic optic neuropathy

2. Define algorithm for re-coding the SLEDAI-2K v10Oct2015 values
    a. BILAG ‘New’ or ‘Worse’ or ‘Same’ or ‘Improving’ for any one of the BILAG components included in a specific SLEDAI domain result in a re-coding of a ‘PRESENT’ value for that specific SLEDAI-2K Recode domain.
    b. BILAG ‘Not Present’ or missing for all of the BILAG components in a specific SLEDAI domain = ‘ABSENT’ for that specific SLEDAI-2K Recode domain.
3. Using steps #1-#2 above, re-code the 8 SLEDAI-2K v10Oct2015 domains that did not utilize the 30 day look back as either ‘ABSENT’ or ‘PRESENT’. For the remaining 16 SLEDAI-2K domains, utilize the SLEDAI-2K v10Oct2015 responses as collected.
4. Database the SLEDAI-2K Recode domain values in addition to the original SLEDAI-2K v10Oct2015 responses to be used in exploratory analyses
5. Utilize the 8 SLEDAI-2K Recode domain values in addition to the original 16 SLEDAI-2K v10Oct2015 responses to calculate a new variable, SLEDAI-2K Recode Total Score.

5.5.2. Analysis Specifications

5.5.2.1. SLEDAI-2K v10Oct2015 (modified SLEDAI-2K)

For the purposes of this SAP, ALL analyses referencing SLEDAI-2K are those based upon the **modified** SLEDAI-2K and will be performed as outlined in this SAP.

5.5.2.2. SLEDAI-2K Re-Code

The following analyses will be performed utilizing the SLEDAI-2K Re-Code data.

SRI-4 Composite Response at Week 52 Using SLEDAI-2K Re-Code: Defined as ≥4-point reduction from baseline in SLEDAI-2K Re-Code score, no new BILAG A and no more than 1 new BILAG B domain score, and no worsening from baseline in the Physician's Global Assessment (PGA) of Disease Activity (<10% worsening from baseline). For the primary endpoint analysis, SRI-4 composite response is the proportion of subjects who achieve a response at Week 52 and do not meet treatment failure criteria to Week 52.

Sensitivity Analysis 1 (Treatment Policy Estimand) Using SLEDAI-2K Re-Code: Sensitivity analysis #1B, see Section 5.2.3.2, will be performed on the population of subjects who have Week 52 SLEDAI-2K Re-Code data.

Sensitivity Analysis 2 (Primary Estimand) Using SLEDAI-2K Re-Code: Sensitivity analysis #2, see Section 5.2.3.2, based upon the entire FAS will be performed on the population of subjects who have Week 52 SLEDAI-2K Re-Code data.

5.5.3. Analysis Methods

Unless otherwise stated, the analysis population for the SLEDAI-2K Re-Code analysis will be the FAS excluding those subjects whose projected Week 52 visit occurs after study termination as defined in Section 2.3.2. The endpoints will be summarized by treatment groups.

P-values provided will be nominal.

Binary endpoints (e.g. responder analysis) will be analyzed using the same approach as the primary endpoint. Logistic regression, adjusting for baseline stratification factors, region and baseline SLEDAI-2K score (continuous variable) as described in Section 5.2.3 will be used.

Consistency across the analyses may be displayed graphically.

6. SAFETY

Unless otherwise stated, all safety analyses will be based upon the safety analysis set as described in Section 2.3.3 above. No formal statistical comparison is planned.

6.1. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study agent is considered to be a treatment emergent adverse event (TEAE). If the event occurs on the day of the initial administration of study agent, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study agent based on partial onset date or resolution date. AEs that occur prior to the administration of study agent but then increase in intensity after dosing are also considered to be treatment emergent. All reported treatment-emergent adverse events will be included in the

analysis. For each adverse event, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

TEAEs will be tabulated by treatment group and Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and be sorted in descending frequency of the Preferred Term (PT) within the SOC. The following TEAEs will be summarized by treatment group:

Summary tables will be provided for:

- All TEAEs
- Serious TEAEs
- TEAEs reasonably related to study agent
- TEAEs by severity (mild, moderate, severe)
- Treatment emergent infections including serious infections
- Treatment emergent opportunistic infection
- Treatment emergent infusion/injection site reactions
- Treatment emergent hypersensitivity reactions
- Treatment emergent occurrences of Tuberculosis

In addition to the summary tables, the following will be listed by subject:

- Serious TEAEs
- TEAEs leading to discontinuation of study agent
- Major Adverse Cardiovascular Events (MACE)
- Any deaths

A reasonably related AE is defined as any event with the relationship to study agent as ‘very likely’, ‘probable’, or ‘possible’ on the AE eCRF page or if the relationship to study agent is missing.

Infusion reaction is defined as the following:

Refer only to the adverse event dataset. An infusion reaction is defined as an AE that occurs during or within 1 hour following the infusion of study agent and the event must be included within the MedDRA narrow Hypersensitivity Reactions SMQ, with the exception of laboratory abnormalities.

Use the following rationale to exclude lab abnormality events:

Exclude all AEs coded to the SOC of Investigations with the exception of the following 2 Higher Level Grouped Terms (HLGTs). Include only the following 2 HLGTs from the Investigation SOC as infusion reactions:

- Cardiac and vascular investigations (excl enzyme tests)
- Physical examination and organ system status topics

If the AE onset time is missing and the AE onset date is the same as the infusion date, the missing time will be imputed with the time of the infusion

An injection site reaction is defined as an AE with the question on the AE eCRF page 'Was this an injection site reaction' = 'Yes'.

An infection is defined as any AE that was characterized by the investigator as an infection on the eCRF.

An opportunistic infection is defined as infection by an organism that normally is not pathogenic or does not cause invasive infection in immunocompetent hosts (e.g. cytomegalovirus, pneumocystosis, or aspergillosis).

Since safety should be assessed relative to exposure and follow-up, all AE summary tables will summarize the average weeks of follow-up and average exposure for each treatment group.

6.2. Clinical Laboratory Tests

Routine laboratory data from clinical chemistry, hematology, serology and urinalysis will be collected at screening and at Visits according to the time and events schedule in the study protocol. The laboratory data to be summarized are as follows:

Clinical Blood Chemistry: Chemistry panel including alanine aminotransferase (ALT), albumin, aldolase (if creatinine kinase is elevated at screening then perform aldolase test at screening, Week 0 and follow-up as needed), alkaline phosphatase, aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, creatinine kinase, FSH as needed, glucose (non-fasting), phosphorous, potassium, sodium, total bilirubin, total protein. If total bilirubin is abnormally elevated, both direct and indirect bilirubin will be assessed.

Hematology: hemoglobin, hematocrit, platelet count, white blood cell (WBC) total and differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils), CD19 B-cell analyses by flow cytometry during screening only if needed for subjects previously exposed to B-cell depleting therapies, Coomb's direct test

Coagulation Laboratories: prothrombin time (PT), partial prothrombin time (PTT), international normalized ratio (INR)

Urinalysis: Dipstick (bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, specific gravity, and urobilinogen), urine sediment microscopy (bacteria, crystals, epithelial cells, granular casts, heme casts, RBC, RBC casts, WBC, WBC casts) and urinary protein/creatinine ratio

Additional lab data may be summarized as needed.

Descriptive statistics for selected clinical laboratory analyte and for change from baseline at each scheduled post-baseline visit will be provided by treatment group. The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 4.0) will be used in the summary of laboratory data (Grade 0-4). The proportion of subjects with post-baseline values by maximum toxicity grade for clinical laboratory tests will be summarized by treatment group. Subjects with toxicity grades ≥ 2 will be listed.

Proportion of subjects with maximum ALT/AST will be provided for the categories:

- 1 to < 2xULN
- ≥ 2 to < 3xULN
- ≥ 3 to < 5xULN
- ≥ 5xULN

For those labs without CTCAE toxicity grades, the incidence of markedly abnormal laboratory values will be presented by treatment group. Additionally, the markedly abnormal laboratory values will be listed. Markedly abnormal criteria will be defined in the Data Presentation Specifications (DPS) document.

6.3. Vital Signs and Physical Examination Findings

Weight, blood pressure, temperature, respiratory rate and heart rate will be assessed with a completely automated device.

Descriptive statistics of changes from baseline will be summarized by visit and treatment group. Abnormal findings will be summarized by treatment group. In addition, a listing of subjects with abnormal vital signs will be presented. Vital sign parameters will be considered abnormal using the criteria below:

Vital Sign	Abnormally Low	Abnormally High
Systolic BP (mm Hg)	Absolute value < 90 mmHg and a decrease from baseline ≥ 20 mmHg	Absolute value > 180 mmHg and an increase from baseline ≥ 20 mmHg
Diastolic BP (mm Hg)	Absolute value < 50 mmHg and a decrease from baseline ≥ 15 mm Hg	Absolute value > 105 and an increase from baseline ≥ 15 mm Hg
Respiratory Rate (beats/minute)	< 12	> 24
Heart Rate (beats/minute)	Absolute value < 50 bpm and a decrease from baseline ≥ 15 bpm	Absolute value > 120 bpm and an increase from baseline ≥ 15 bpm
Temperature (°C)	< 36°C	> 38°C

6.4. Electrocardiogram

This section does not apply to this study.

6.5. Other Safety Parameters

This section does not apply to this study.

6.6. COVID-19 Summaries

Included in the adverse event summaries discussed in this section will be events related to COVID-19. These will be identified and coded using the MedDRA coding guidance for COVID-19. Summary tables will be provided for:

- COVID-19 related TEAEs
- Selected TEAEs of interest related to COVID-19
- Selected TEAEs of interest related to COVID-19

In addition to the summary tables, the following will be listed by subject:

- TEAEs related to COVID-19
- Serious TEAEs related to COVID-19
- Deaths related to COVID-19

7. PHARMACOKINETICS/PHARMACODYNAMICS

7.1. Pharmacokinetics

PK analyses will be performed on the PK analysis set (see Section 2.3.4). No imputation for missing concentration data will be performed.

PK concentrations will be summarized by treatment group among PK evaluable subjects. Descriptive statistics, including arithmetic mean, SD, coefficient of variation, median, minimum, and maximum will be calculated for ustekinumab concentrations at each sampling time.

Concentrations below the lowest quantifiable concentration in a sample will be treated as zero in the summary statistics. All subjects excluded from the analysis will be clearly documented in the study report. Once a subject meets one of the following dosing deviation criteria, the subject's data will be excluded from the by-visit data analyses from that point onwards:

- Discontinued ustekinumab administrations.
- Skipped an ustekinumab administration.
- Received an incomplete/ incorrect ustekinumab dose.
- Received an incorrect study agent.
- Received an additional ustekinumab dose.
- Received an administration outside of visit windows (For PK analyses, the visit and the study agent administration should occur within +/- 7 days of the scheduled visit day relative to Week 0).

The definition of treatment group at Week 52 analysis is as follows:

- **Ustekinumab:** Subjects who received ustekinumab at any time from Week 0.

PK data may be displayed graphically. Plots of mean (SD) serum concentrations of ustekinumab over time, using semi-logarithmic scales, may be provided.

The relationship between PK and antibody to ustekinumab status may be assessed.

If feasible, a population PK analysis using nonlinear mixed effects modeling may be used to characterize the disposition characteristics of ustekinumab in the current study. The influence of important variables such as body weight and antibodies to ustekinumab status on the population PK parameter estimates may be evaluated. Details will be given in a population PK analysis plan, and results of the population PK analysis will be presented in a separate technical report.

7.2. Immune Response

Blood samples will be collected to examine the formation of antibodies to ustekinumab at the specified visits as shown in the schedule of events in the protocol. For subjects who discontinue study agent administrations, samples will be collected at their final safety visit, 16 weeks after the last study agent administration.

The data analysis includes the following:

- The incidence and titers of antibodies to ustekinumab will be summarized for all subjects who received at least one dose of ustekinumab and had appropriate serum samples for antibody detection.

- The incidence of neutralizing antibody status (NAbs) to ustekinumab will be summarized for subjects who are positive for antibodies to ustekinumab and have samples evaluable for NAbs.
- A listing of subjects positive for antibodies to ustekinumab at any time.
- The relationship between antibody to ustekinumab and efficacy at Week 52 (SRI-4 composite response).
- Infusion/injection-site reactions by antibody to ustekinumab status and treatment group.

The definition of treatment group at Week 52 analysis is as follows:

- **Ustekinumab:** Subjects who received ustekinumab at any time from Week 0.

7.3. Pharmacodynamics

Anti-Nuclear Antibody (ANA) levels and proportion of subjects with positive ANA over time will be summarized for those subjects positive at baseline.

Changes in the concentration and proportion of subjects with abnormalities of individual pharmacodynamics markers from baseline to the selected post treatment time points will be summarized. These include but are not limited to ANA, anti-ds-DNA, C3 and C4 complement, IgA, IgG, and IgM.

7.4. Pharmacokinetic/Pharmacodynamic Relationships

If data permit, the relationships between serum ustekinumab concentration and efficacy or pharmacodynamic measures may be analyzed graphically.

8. LONG TERM EXTENSION (THROUGH WEEK 176) SUMMARIES

Eligible subjects could enter the study extension after their Week 52 visit. However, due to the early termination of the study a formal Week 176 DBL (i.e. the end of the extension period of the study) will not occur. The following summaries are to evaluate the entirety of safety data for the trial through the trial termination and 16 weeks of safety follow up as well as demographics and disposition for those subjects entering the study extension.

There is no formal statistical hypothesis testing for the Week 176 DBL, neither are there efficacy summaries after Week 52. Due to the early termination of the trial, the data from the Week 176 DBL are supportive to Week 52 and will evaluate longer term safety.

8.1. Demographics

Demographics and baseline characteristics for those subjects entering the study extension will be summarized based upon the randomized analysis set.

8.2. Disposition

Disposition information will be summarized by treatment group in terms of numbers of subjects randomized, treated, entering study extension and completing scheduled study extension visits.

Disposition information will be based upon the randomized analysis set. Additionally, the number of subjects who discontinued study agent after entering the study extension and the reason for discontinuation as well as those who terminated the study and reason for termination will be summarized.

8.3. Protocol Deviations

Protocol deviations will be summarized as described in Section 4.5.

8.4. Concomitant Medications

Concomitant medications will be summarized as described in Section 4.6.

8.5. Efficacy

Efficacy data after Week 52 will not be summarized.

8.6. Adverse Events

Adverse Events (AEs) will be summarized in similar fashion as described in Section 6.1.

For the placebo group, AEs that occur before entering the LTE and receiving the first dose of ustekinumab (before entering LTE) will be considered to have occurred while on placebo treatment. AEs that occur in the placebo group during or after the first dose of ustekinumab (after entering LTE and receiving first dose of ustekinumab) will be considered to have occurred while on ustekinumab treatment. Summaries will clearly describe this separation (e.g. example heading below).

Placebo – Ustekinumab	
Placebo (Before LTE Entry)	Ustekinumab (After LTE Entry)

8.7. Clinical Laboratory Tests

Clinical labs will be summarized as described in Section 6.2.

8.8. Vital Signs and Physical Examination Findings

Vital signs will be summarized as described in Section 6.3.

8.9. Pharmacokinetics/Immunogenicity/Pharmacodynamics

PK and immunogenicity will be summarized as described in Sections 7.1 and 7.2 excluding any analysis of efficacy and immune response.

REFERENCES

1. Agresti A, Coul BA. Approximate is Better than Exact for Interval Estimation of Binomial Proportions. The American Statistician, 2013; 52(2): 119-126.
2. Albrecht J, Taylor L, Berlin JA, et al. The CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index): an outcome instrument for cutaneous lupus erythematosus. J Invest Dermatol. 2005;125(5):889-894.
3. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum. 1995;38(6):727-735.
4. Furie RA, Petri MA, Wallace DJ, et al. Novel evidence-based systemic lupus erythematosus responder index. Arthritis Rheum. 2009;61(9):1143-1151.
5. Hay EM, Bacon PA, Gordon C, et al. The BILAG index: a reliable and valid instrument for measuring clinical disease activity in systemic lupus erythematosus. Quart J Medicine. 1993;86:447-458.
6. Isenberg DA, Rahman A, Allen E, et al. BILAG 2004. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. Rheumatology. 2005;44:902-906.
7. Touma Z, Gladman DD, Urowitz MB. SLEDAI-2K for a 30 day window. Lupus. 2010a;19(1):49-51. Epub 2009 Nov 12.
8. Touma Z; Urowitz M, Gladman D. SLEDAI-2K Responder Index-50 (SRI-50). Lupus. The 9th International Congress on SLE June 24-27 2010b, Vancouver, Canada. Abstract PO2.D.7.
9. van Vollenhoven R, Hahn BH, Tsokos GC, et al. Efficacy and safety of ustekinumab, an interleukin 12/23 inhibitor, in patients with active systemic lupus erythematosus: results of a Phase 2, randomized placebo-controlled study [abstract]. Arthritis Rheumatol. 2017; 69 (suppl 10). http://acrabstracts.org/abstract/efficacy-and-safety-of-ustekinumab-an-interleukin-1223-inhibitor-in-patients-with-active-systemic-lupus-erythematosus-results-of-a-phase-2-randomized-placebo-controlled-study/. Accessed November 28, 2017.