Janssen Research & Development *

Clinical Protocol

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

Protocol CNTO1275SLE3001 Amendment 2; Phase 3
AMENDMENT 2

STELARA® (ustekinumab)

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

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

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	11 December 2017
Amendment 1	15 February 2018
Amendment 2	23 Jan 2019

Amendments below are listed beginning with the most recent amendment.

Amendment 2 (23 Jan 2019)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is to add, based on input from the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), a site visit at the beginning of the extension period in order to more closely monitor subjects crossing over from placebo to ustekinumab. Additional clarifications to the protocol have been implemented as well based on feedback from the United States Food and Drug Administration (FDA), key opinion leaders, and study investigators.

Applicable Section(s)	Description of Change(s)
Rationale: The extension period will now begin at Week 56 (instead of at Week 56 **o**r Week 64) and the Week 64 visit will become a mandatory site visit in order to more closely monitor subjects crossing over from placebo to ustekinumab.	
Synopsis, Dosage and Administration; 6. Dosage and Administration; 9.1.4. Extension Period; 9.1.4.2. Dosing Regimen	(*Deleted text is struck-through and new text is in bold and underlined):* During the extension period beginning at ~~either~~ Week 56 ~~or Week 64~~.
Time and Events Schedule – Screening Period and 52-Week Double-blind Period	Footnote c revised: c. **Mandatory at-site visit for subjects who enter the study extension**. ~~Subjects who will participate in the extension period do not need to return for the Week 64 visit.~~
Time and Events Schedule – Extension Period	Week 56 and Week 64 visits have been separated into new columns in Table 2 Time and Events Schedule and footnote b revised: b**. Mandatory at-site visit for subjects who enter the study extension.** ~~There will be a window to enter the extension at either Week 56 or Week 64. Subjects who enter the extension period should follow the Time and Events procedures outlined for "Week 56 or Week 64" in the table of Extension procedures (Table 2).~~
3.1 Overview of Study Design	Figure 1 revised to reflect change in visits.

Applicable Section(s)	Description of Change(s)
Rationale: The Week 80 visit (Extension Period) has been changed from an at-home to an at-site visit for all subjects. This change was made to better assess efficacy and safety in subjects randomized to placebo 24 weeks following their crossover to ustekinumab in the extension period. This allows better comparability with subjects randomized to ustekinumab in the double-blind period. Reciprocally, the Week 88 visit was changed from an at-site to an at-home visit.	
Time and Events Schedule – Extension Period	Column heading under "Week" changed from 88 to 80.
Rationale: Text was corrected to remove mention of consent/assent requirement for whole blood gene expression analysis by RNA sequencing since RNA sequencing will not be performed.	
Time and Events Schedule: Screening Period and 52-week double-blind period, footnotes e and f	~~whole blood gene expression analysis by RNA sequencing~~
Rationale: Detailed treatment failure criteria were added at the request of the FDA.	
11.4.5. Treatment Failure Criteria	A new section detailing treatment failure criteria was added.

Applicable Section(s)	Description of Change(s)

Rationale: Endpoints have been modified, added, or removed based on input from key opinion leaders to enhance the value of the data obtained. In addition, the endpoints for certain PROs (for which validated definitions for clinically meaningful improvement do not exist) were revised to clarify that change from baseline, not clinically meaningful improvement from baseline, is being assessed. These endpoints were grouped into a separate bullet.

2.2.3 Additional Endpoints

Measures of Improvement in Global Disease Activity

- The proportions of subjects with SRI-4, SRI-5, SRI-6, SRI-7, and SRI-8 composite **responses**~~, sustained composite response~~ over time
- **The proportion of subjects with an SRI-4 composite response at ≥50% of the study visits from baseline to Week 52**
- **The proportion of subjects with at least a 4-point improvement compared with baseline in S2K RI-50 over time**

Mucocutaneous Disease

- **The proportion of subjects who achieve a 20% or 50% reduction from baseline in CLASI activity score over time in those with a baseline CLASI activity score of at least 8**

Assessment of Organ Domain Activity and Damage

- The proportion of subjects with ~~BILAG worsening,~~ no BILAG worsening compared with baseline over time
- ~~Time to first CLASI damage score worsening (defined as CLASI damage score >0) in those subjects with CLASI damage score = 0 at baseline~~
- ~~Proportion of subjects who remain free of CLASI damage progression (defined as CLASI damage score = 0) over time~~
- ~~Proportion of subjects with CLASI damage accrual (defined as change from baseline in CLASI damage score >0) over time~~

Disease-specific Clinical Biomarkers

- The proportions of subjects with normalization, improvement of anti-dsDNA **and other** autoantibodies, C3, C4 levels over time in subjects with abnormal levels of that serologic marker at baseline*

Patient-reported Outcomes/ Health Economics and Outcomes Research

- The proportion of subjects with clinically meaningful improvement in patient-reported outcomes (PROs) over time: pain visual analogue scale (VAS),* Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-Fatigue), 36-Item Short Form Health Survey (SF-36v2; physical component score [PCS], mental component score [MCS], both PCS and MCS, individual domains), ~~EuroQol 5-dimensional, 5-level questionnaire (EQ-5D-5L) index score and VAS score,*~~ Lupus Quality of Life (LupusQoL) domain scores,* ~~Work Productivity and Activity Impairment Questionnaire-Lupus (WPAI-Lupus) total and domain scores, LFA-REAL PRO*~~
- Change from baseline in PROs over time: EuroQol 5-dimensional, 5-level questionnaire (EQ-5D-5L) index score and VAS score,* Work Productivity and Activity Impairment Questionnaire–Lupus (WPAI-Lupus) total and domain scores, LFA-REAL PRO*

Applicable Section(s)	Description of Change(s)
Rationale: It was clarified that the results of certain exploratory assessments will be summarized in a separate report	
Synopsis, Efficacy Evaluations; 2.2.3 Additional Endpoints	Certain efficacy evaluations and exploratory endpoints were asterisked and the following note added to the section: *** Results of these exploratory assessments will be summarized in a separate report.**
Rationale: Inclusion/Exclusion Criteria and Prohibitions and Restrictions were clarified/added in order to enhance subject safety and/or the quality of the trial.	
4.1.1 Inclusion Criteria, #6	**6.1** Had a documented medical history **(ie, met at least 1 of the bulleted criteria below)** that subject met the SLICC classification criteria for SLE[41] ~~(meeting at least 4 SLICC criteria in total including at least 1 immunologic criteria; Attachment 1)~~ at least 3 months prior to first dose of study agent: • **Met a total of at least 4 SLICC criteria, including at least 1 immunologic and at least 1 clinical (Attachment 1).** • **Had a diagnosis of lupus nephritis, confirmed by renal biopsy, and at least 1 of the following autoantibodies: ANA or anti-dsDNA**.
4.1.2 Exclusion Criteria, #1	Criterion modified per Amendment 2: 1.1 Has any unstable or progressive manifestation of SLE (lupus cerebritis, optic neuritis, transverse myelitis, psychosis, uncontrolled seizures, systemic vasculitis, end-stage renal disease, severe or rapidly progressive Class III or IV glomerulonephritis, isolated Class V lupus nephritis [ie, without coexistent Class I, II, III, or IV nephritis], Class VI lupus nephritis, pulmonary hemorrhage, myocarditis) that is likely to warrant escalation in therapy beyond permitted background medications. **Subjects requiring renal hemodialysis or peritoneal dialysis are also excluded.**
Exclusion Criteria, #45	**45. Has undergone a splenectomy.**
4.2 Prohibitions and Restrictions, #3	Agree **to avoid excess exposure to natural or artificial (tanning beds, phototherapy, etc) sunlight. In addition, it is advised that subjects maintain their typical** use **of** sun protective measures (such as a hat, sunglasses, protective clothing, sunscreen)~~., limit prolonged exposure to natural sunlight, and avoid artificial sunlight (tanning beds or phototherapy) from baseline~~. **The time period for this requirement is from the start of screening** until the last dose of study agent has been received.

Applicable Section(s)	Description of Change(s)
Rationale: Text describing prestudy and concomitant medication requirements has been clarified to enhance subject safety and/or the quality of the trial.	
4.1.2 Exclusion Criteria	
Exclusion Criteria, #8	**Criterion modified per Amendment 2:** **8.1** Exclusions for treatment with B-cell targeted therapies (eg, belimumab, rituximab, epratuzumab)* are as follows: a. Treatment with a single B-cell targeted therapy within 3 months prior to first dose of study agent. b. Treatment with >1 previous B-cell targeted therapy within 6 months prior to first dose of study agent. c. Treatment with B-cell depleting therapy (eg, rituximab, epratuzumab) within 12 months prior to first dose of study agent or have evidence of continued B-cell depletion following such therapy. ***If a subject has received one or more B-cell targeted therapies, the length of time required before administering the first dose of study agent should be whichever is the longest applicable washout period.**
Exclusion Criteria, #12	**Criterion modified per Amendment 2:** **12.1** Has received topical cream/ointment preparations of cyclosporine A (except for ophthalmic use), **high-potency topical glucocorticoids (World Health Organization [WHO] encoding dictionary),** or other topical immunomodulatory agents (such as tacrolimus, pimecrolimus) within 4 weeks prior to the first administration of study agent.
8.1 Prestudy and Concomitant Medications Through Week 52, Table 4	Revised column header to be consistent with other references to concomitant medication use (*Deleted text is struck-through and new text is in bold and underlined):* Stabilization Period ~~Before Randomization~~ **Prior to First Administration of Study Agent**
8.1.2 Glucocorticoid Therapy, Epidural, Intravenous, Intramuscular, Intra-articular, Intrabursal injection, and Intralesional Glucocorticoids	If clinically necessary, a total of 1 or 2 IA injections may be permitted for SLE up to ~~the~~ Week 12 ~~dosing~~ **and should be recorded as a medical procedure**; however, joints treated with IA injections ~~should~~ **will** be ~~considered~~ **imputed as** "active" in all subsequent assessments. **After Week 12, IA glucocorticoid use may also cause subjects to be considered treatment failures**.
8.1.3. Nonsteroidal Anti-inflammatory Drugs	Subjects are permitted to receive the usual marketed doses approved in the country in which the study is being conducted. NSAIDs, including aspirin or selective cyclooxygenase-2 (COX-2) inhibitors, and other analgesics (including topical or injectable NSAIDs, analgesics or other pain-relieving agents such as capsaicin) **that are used on an "as needed" basis** should not be used within 48 hours before a study visit.

Applicable Section(s)	Description of Change(s)
8.1.6 Topical Medications	**Regular use of** topical medications **is** permitted. However, topical compounds cannot include a prohibited medication. For example, topical ointments or creams of cyclosporine A, tacrolimus, ~~or~~ pimecrolimus, **dapsone, thalidomide, etc,** are prohibited through Week 52; however, ophthalmic use of cyclosporine A is permitted. **"As needed" use of** topical NSAIDs, analgesics, or other pain-relieving agents such as capsaicin ~~cannot be used for~~ **is permitted, but not within** 48 hours prior to study visit. **"As needed" use of** topical low (Class VI, VII) to moderate (Class IV, Class V) potency glucocorticoids (according to the World Health Organization **(WHO)** classification of topical glucocorticoids) ~~are permitted but should not be used for~~ **is permitted, but not within** 48 hours prior to a study visit. High potency topical glucocorticoids are not allowed through Week 52 for all subjects with cutaneous involvement.
Rationale: "Active" joints and joint assessments were further defined for greater clarity.	
9.2.5 Joint Count Assessments	Assessment of active joints (defined as joints demonstrating pain and signs of inflammation), tender joints, and swollen joints will be performed at visits indicated in Table 1 and Table 2. **To be considered an active joint, an affected joint must be painful as reported by the subject and must demonstrate tenderness and at least one additional sign of inflammation (eg, observed swelling such as edema or effusion) on physical examination as determined by the joint assessor.** Each of 64 joints will be evaluated for tenderness and 62 joints for swelling (hips are excluded for swelling). The joint assessment should be performed by an adequately trained joint assessor. **The joint assessor should preferably be a rheumatologist, but if a rheumatologist is not available, it should be a health care provider with at least 1 year of experience in performing joint assessments. A health care provider with less than 1 year of experience may serve as a joint assessor based upon the approval of the sponsor.** It is strongly recommended that the same joint assessor perform these assessments at every visit. It is recommended that the designated assessor identify an appropriate back-up joint assessor in case the designated joint assessor is unavailable.
Rationale: Revisions were made to clarify the qualifications required for ClinRO assessors.	
Time and Events Schedule – Screening Period and 52-Week Double-blind Period, Footnote q.	q. Whenever possible, patient-reported outcome assessments should be conducted before any tests, procedures, or other consultations for that visit to prevent influencing subjects' perceptions. It is recommended that PROs be performed in the following sequence: Patient Assessment of Pain Intensity (VAS), FACIT-Fatigue, SF-36, EQ-5D-5L, LupusQoL, WPAI-Lupus, and LFA-REAL PRO. It is recommended that ClinRO procedures be performed in the following sequence: BILAG, SLEDAI-2K, mSFI, PGA, joint count assessment, CLASI, LFA-REAL ClinRO, and SLICC/ACR Damage Index. **ClinRO assessments should be performed by an adequately trained assessor (see Section 9.2 for details).**

Applicable Section(s)	Description of Change(s)
Time and Events Schedule – Extension Period, Footnote i.	i. Whenever possible, patient-reported outcome assessments should be conducted before any tests, procedures, or other consultations for that visit to prevent influencing subjects' perceptions. It is recommended that PROs be performed in the following sequence: FACIT-Fatigue, SF-36, and WPAI-Lupus. It is recommended that ClinRO procedures be performed in the following sequence: BILAG, SLEDAI-2K, PGA, joint count assessment, CLASI, and SLICC/ACR Damage Index. **ClinRO assessments should be performed by an adequately trained assessor (see Section 9.2 for details)**.
9.1.1 Study Overview	It is recommended that PROs be performed in the following sequence: Patient Assessment of Pain Intensity (VAS), FACIT-Fatigue, SF-36, EQ-5D-5L, LupusQoL, WPAI-Lupus, and LFA-REAL PRO. It is recommended that ClinRO procedures be performed in the following sequence: BILAG, SLEDAI-2K, mSFI, PGA, joint count assessment, CLASI, LFA-REAL ClinRO, and SLICC/ACR Damage Index. **ClinRO assessments should be performed by an adequately trained assessor (see Section 9.2 for details).**
9.2 Efficacy Evaluations	All efficacy evaluations should be performed consistently by the same study Investigator or subinvestigator **at every visit** to achieve comparable measures over time. **It is recommended that the designated assessor identify an appropriate backup in case the designated assessor is unavailable.** **ClinROs, including joint assessments, should be performed by an adequately trained assessor, preferably a rheumatologist. If a rheumatologist is not available, the assessor should be a health care provider with at least 1 year of experience in scoring these instruments. A health care provider with less than 1 year of experience may serve as a ClinRO assessor only with the approval of the sponsor. It is recommended that the designated assessor identify an appropriate backup.**
Rationale: Text listing the serum chemistry panel to be collected has been revised to clarify that an aldolase reflex test should also be allowed at screening.	
9.7.2. Clinical Laboratory Tests, Serum Chemistry Panel	-Aldolase (if creatine kinase is elevated at screening then **perform** aldolase test at **screening**, Week 0, and follow-up as needed)
Rationale: Revisions were made to screening period wording to ensure consistency of concept in the protocol.	
4. Subject Population	Screening for eligible subjects must be performed **no more than 6 weeks prior to the randomization visit (Week 0)**~~.within 6 weeks before the first administration of the study agent.~~
Rationale: Revisions were made to retesting/rescreening wording to clarify that 1) retesting for ANA, anti-dsDNA, anti-Smith is also permitted; 2) that local laboratories are not permitted to substitute for central lab testing; and 3) that rescreening should be discussed with the sponsor.	
4.1.1 Inclusion Criteria, #19; 9.1.2.1. Retesting/Rescreening	A one-time repeat of screening laboratory tests (eg, hemoglobin, lymphocytes, neutrophils, platelets, serum creatinine, AST, ~~and~~ ALT, **ANA, anti-dsDNA, anti-Smith**) is allowed during the 6-week screening period and the Investigator may consider the subject eligible if the previously **exclusionary** laboratory test result is within an acceptable range **per eligibility criteria** on repeat testing at the central laboratory. …

Applicable Section(s)	Description of Change(s)
	~~A request to use a local laboratory test to replace the central laboratory test should be discussed with the medical monitor prior to retesting.~~ … **If the investigator wishes to rescreen a subject who has failed screening, the investigator should discuss it with the study sponsor and/or their designee. Only 1 rescreening is allowed per subject.** ~~If a subject is a screen failure, the subject may be rescreened 1 additional time after a period of at least 30 days.~~ Subjects who are rescreened will be assigned a new subject number, undergo the informed consent process again, and start a new screening phase.
Rationale: Text was added to clarify which COAs are collected using paper and which using electronic devices.	
15. Study-Specific Materials.	• Certain Clinical Outcome Assessments (COAs; includes both PROs and ClinROs) will be collected using an electronic device while others will be collected on paper worksheets. Therefore, the following materials will be provided: – COA questionnaires and completion instructions. **The following ClinROs and PROs will be collected on the paper worksheets provided:** o **ClinROs:** ♦ **SLEDAI-2K RI-50** ♦ **BILAG** ♦ **mSFI** ♦ **CLASI** ♦ **LFA REAL – ClinRO portion** ♦ **SLICC/ACR Damage Index** o **PROs:** ♦ **LFA REAL – PRO portion. Collection only in US for native English speakers.** – Electronic COA device and user manual. **The following ClinROs and PROs will be collected using an electronic device:** o **ClinROs:** ♦ **PGA VAS** ♦ **Joint count assessment (used to obtain number of active joints for entry into SLEDAI-2K-RI50)** o **PROs:** ♦ **Patient Assessment of Pain Intensity VAS** ♦ **FACIT-Fatigue** ♦ **SF-36 v2** ♦ **EQ-5D-5L Descriptive System** ♦ **LupusQoL** ♦ **WPAI-Lupus**

Applicable Section(s)	Description of Change(s)
17.4 Source Documentation	~~Subject- and Investigator-completed scales and assessments designated by the sponsor may by be recorded on paper or directly into an electronic device and will be considered source data.~~
Rationale: "Gold" has been removed from the name of the QuantiFERON®-TB test so that the name applies to both the "Gold" and "Gold Plus" tests, and the Attachment describing the QuantiFERON®-TB test has been deleted to keep test references consistent with product name changes.	
Throughout the protocol	QuantiFERON®-TB ~~Gold~~ test
Attachment 2: QuantiFERON®-TB Gold Testing	Entire Attachment deleted and succeeding Attachments renumbered.
Rationale: Text was added to ensure that sites can comply with local standards of practice regarding TB screening.	
Time and Events Schedule – Screening Period and 52-Week Double-blind Period, Footnote l.	TB evaluation includes an assessment of recent exposure or risk of TB including new or chronic cough, fever, night sweats, unintentional weight loss or recent contact with someone with active TB. If TB is suspected at any time during the study, a chest x-ray (performed locally, consistent with local regulations), and QuantiFERON®-TB test should be performed. A TST is additionally required if the QuantiFERON®-TB test is not registered/approved locally or the TST is mandated by local health authorities. **Additional safety procedures may be performed if clinically indicated or mandated by local standards of practice.**
Rationale: Text was revised to clarify training on self-administration of study drug and subject's inability to self-administer study drug at home.	
Table 2 Time & Events Schedule: Extension Period, footnote e;	e. Following training on study agent administration, study agent may be administered by the subject (or trained designee) at home via SC injection every 8 weeks. Subjects will be required to document administered doses in their subject diaries. Subjects who are **unwilling or** unable to self-administer study agent at home (**eg, because they are following standard practice in their country or because recommended storage conditions are not feasible**) are permitted to receive SC injections by a trained designee at the study site or at home.
6 Dosage and Administration;	During the double-blind study period, subjects will be administered study agent at the study site. **Subjects (or their designee) should be trained to administer study agent during the Week 56 and the Week 64 visit of the extension period. Additional training sessions are permitted per Investigator discretion**. During the extension period beginning at ~~either~~ Week 56 ~~or Week 64~~ and continuing to Week 160 (and after appropriate and documented training), subjects will be encouraged to **administer** ~~self-administer~~ study agent at home; study agent will be provided to subjects for at-home administration. Subjects who are **unwilling or** unable to self-administer study agent at home **(eg, because they are following standard practice in their country or because recommended storage conditions are not feasible)** are permitted to receive SC injections at the study site or at home by a trained designee. See Section 14 for further instructions on the IV and SC administration of the study agent. Additional details may be provided in a pharmacy manual/study site investigational product (IP) and procedures manual that is provided separately (Section 15).

Applicable Section(s)	Description of Change(s)
7. Treatment Compliance	During the extension period, if a study visit occurs on the same day that a subject is due to receive his or her next dose, ustekinumab may be administered at the study site. Subjects who are **unwilling or** unable to self-administer ustekinumab **(eg, because they are following standard practice in their country or because recommended storage conditions are not feasible)** may return to the study side for additional visits to have study agent administered. Additional visits to the study site should be documented. Subjects will be required to document in their diaries study agent administered at home (see Section 6).

Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 1 (15 February 2018)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: Based on feedback from the United States Food and Drug Administration (FDA), the randomization algorithm using dynamic allocation has been be changed to permuted block randomization, and region was dropped as a stratification factor. Instead, region will be adjusted for in the statistical models for the primary and major secondary endpoints. Additional clarifications to the protocol have been implemented as well based on feedback from the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), and investigators in Japan and China.

Applicable Section(s)	Description of Change(s)
Rationale: The randomization algorithm using dynamic allocation has been changed to permuted block randomization in accord with FDA feedback. Because of this change, region was deleted as a stratification factor.	
Synopsis Overview of Study Design; 3.1 Overview of Study Design; 3.2.2 Blinding, Control, etc; 5.1 Treatment Allocation	Treatment Allocation was modified as follows (*Deleted text is struck-through and new text is in bold and underlined):* **Permuted block 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 on 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.** ~~Dynamic central randomization will be implemented in conducting this study. Subjects will be assigned to 1 of 2 agent groups based on an algorithm implemented in the interactive web response system (IWRS) before the study. Dynamic central randomization minimizes the imbalance in the distribution of the number of subjects across treatment groups within the levels of each individual stratification factor:~~ ~~Subjects will be stratified by race, region,baseline lupus nephritis, and baseline SLE medications and SLEDAI-2K score (a combined factor).~~ ********** Based on the **computer-generated randomization schedule**~~algorithm~~, the IWRS will assign a unique treatment code, which will dictate the treatment assignment and matching study agent kit for each subject. A detailed description of the ~~dynamic~~**permuted block** allocation ~~procedure and algorithm~~ will be included in the SAP.

Applicable Section(s)	Description of Change(s)
Rationale: Region has been removed as a stratification factor and so was added as an analysis adjustment.	
Synopsis Primary Efficacy Analysis; 11.4 Efficacy Analyses; 11.4.1 Primary Endpoint Analysis;	(*Deleted text is struck-through and new text is in bold and underlined)* Logistic regression, adjusting for baseline stratification~~s~~ **factors, region,** and baseline SLEDAI-2K, will be used to analyze the primary endpoint.
Rationale: Region has been removed as a stratification factor and so was added as an analysis adjustment.	
5.1 Treatment allocation	(*Deleted text is struck-through and new text is in bold and underlined)* ~~Subjects will be stratified by race, region, baseline lupus nephritis, and baseline SLE medications and SLEDAI-2K score (a combined factor).~~ **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 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 criteria above for the category of "high" medications would be included in the "medium" medication category.**
Rationale: In describing the futility analysis, "may" be performed was changed to "will" be performed to clarify that the futility analysis would definitely be performed. In addition, wording describing the timing of the analysis was revised at the request of the FDA.	
Synopsis Overview of Study Design; 3.1 Overview of Study Design; 11.10 Interim Analysis; 11.11 Data Monitoring Committee	(*Deleted text is struck-through and new text is in bold and underlined)* A futility analysis ~~may~~**will** be carried out ~~after approximately 50% of the subjects complete Week 24~~ **24 weeks after approximately 50% of the planned subjects have been randomized**.
Rationale: Endpoints/analyses for glucocorticoid dose reduction were revised to clarify the population being analyzed.	
Synopsis Endpoints; 2.2.2 Secondary Endpoints; 2.2.3 Additional Endpoints;	(*Deleted text is struck-through and new text is in bold and underlined)* 6. The proportion of subjects **receiving glucocorticoids at baseline** ~~with SRI-4 composite response at Week 52 in the subpopulation~~ who achieve~~d~~ reduction in glucocorticoid dose by Week 40**,** ~~and~~ sustain~~ed~~ that reduction through Week 52, **and achieve an SRI-4 composite response at Week 52**

Applicable Section(s)	Description of Change(s)
Rationale: Certain exclusion criteria were added or revised to clarify meaning.	
Section 4.1.2 Exclusion Criteria:	(*Deleted text is struck-through and new text is in bold and underlined)*
Criterion 17	*Expanded for greater clarity:* ~~Use of traditional/oriental medicines, herbs, acupuncture, or ointments are prohibited during the study~~. Use of complementary therapies, including traditional/Chinese medicines, herbs, ointments, or procedures (eg, acupuncture), that have the potential to activate (eg, echinacea) or inhibit (eg, *Tripterygium wilfordii* Hook F) the immune system is prohibited within 6 weeks of the first administration of study agent. In addition, use of complementary therapies, including traditional/Chinese medicines, herbs, that have the potential to interact with antithrombotic agents (eg, St. John's Wort) is prohibited within 6 weeks of the first administration of study agent in those taking antithrombotic agents. Any questions or concerns with the use of these therapies should be discussed with the study sponsor and/or medical monitor. **NOTE: See also Exclusion 43 and Exclusion 44.** *Added based on feedback from PMDA:* **Additional concomitant or previous medical therapies received**:
Criterion 43	**Use of IV gamma globulin, apheresis therapy (including but not limited to plasmapheresis, photopheresis, leukocytapheresis), or immunoadsorption is prohibited within 6 months prior to the first administration of study agent and within 4 months after receiving the last administration of study agent**.
Criterion 44	*Added based on feedback from experts in Asia:* **Has ever received stem cell transplantation (including hematopoietic stem cell transplantation and mesenchymal stem cell transplantation).**
Rationale: Interleukin-2 was added as a prohibited therapy based on feedback from experts in Asia	
4.1.2 Exclusion Criteria, Criterion 10; 8.1.7 Prohibited Therapies	(*New text is in bold and underlined)* **Interleukin-2 inhibitors or exogenous IL-2 therapy**
Rationale: Language describing the use of complementary therapies was revised to clarify its meaning.	
8.1.7 Prohibited Therapies	(*Deleted text is struck-through and new text is in bold and underlined)* The use of complementary therapies~~ that may trigger activation of lupus or mitigate the symptoms of SLE, including traditional Chinese medicine (eg, herbal/alternative preparations) is prohibited (see Section 4.1.2).~~ **(eg, herbs, ointments, traditional Chinese medicine, acupuncture) that have the potential to activate or inhibit the immune system is prohibited (see Section 4.1.2). In addition, use of complementary therapies that have the potential to interact with antithrombotic agents is prohibited in those taking antithrombotic agents.** **The use of other complementary therapies is strongly discouraged; in individual cases, use may be permitted following discussion with the study sponsor and/or medical monitor.**

Applicable Section(s)	Description of Change(s)
Rationale: Text was revised to ensure a consistent description of subject options if the subject cannot self-administer study drug at home.	
Table 2 Time & Events Schedule, footnote e; 6 Dosage and Administration; 7. Treatment Compliance; 9.1.4.2 Dosing Regimen	(*Deleted text is struck-through and new text is in bold and underlined)* Following training on study agent administration, study agent may be administered by the subject (or trained designee) at home via SC injection every 8 weeks. Subjects will be required to document ~~the self-~~administered doses in their subject diaries. Subjects who are unable to self-administer study agent at home are permitted to receive SC injections **by a trained designee** at the study site or **at home**~~by trained personnel employed by a home healthcare agency~~.
Rationale: Text was revised to ensure a consistent description of the CLASI activity score enrollment requirement.	
Synopsis Subject Population; 3.2.1 Study Population	(*Deleted text is struck-through)* Additionally, subjects must have a CLASI activity score of at least 4 (excluding diffuse non-inflammatory alopecia)~~at screening and confirmed at Week 0~~ or at least 4 joints with pain and signs of inflammation (active joints) at screening, or at Week 0, or both.
Rationale: Text was revised to clarify that biomarker collection may not occur at all sites.	
3.2.3 Biomarker Collection	(*New text is in bold and underlined)* Biomarker samples will be collected **at selected sites** to evaluate the mechanism of action of ustekinumab to help explain interindividual variability in clinical outcomes, or to help identify population subgroups that respond differently to ustekinumab.
Rationale: Text was revised to clarify that subjects must be able to read and write and give informed consent/assent without assistance to be eligible for study participation.	
16.2.3 Informed Consent and Assent Form	(*Deleted text is struck-through and new text is in bold and underlined)* ~~If the subject (or legally acceptable representative) is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject (or legally acceptable representative) is obtained.~~ ~~Children (minors) or subjects who are unable to comprehend the information provided can be enrolled only after obtaining consent of a legally acceptable representative.~~ Assent must be obtained from children (minors) capable of understanding the nature of the study, depending on the institutional policies. ~~Written assent should be obtained from subjects who are able to write.~~ A separate assent form written in language the subject can understand should be developed for subjects who are not considered to be adults legally (per local requirements). After having obtained the assent, a copy of the assent form must be given to the subject, and to the subject's parent or, if applicable, legally acceptable representative. **Subjects must be able to read and write and give informed consent/assent without assistance. A subject who is unable to read or write or to give informed consent/assent is not eligible to participate in the study.**

Applicable Section(s)	Description of Change(s)
Rationale: Editorial revisions were made to clarify the classification of endpoints and analyses. "Exploratory" used as a description of endpoints/analyses was changed to "Additional" and text was modified to be consistent with this change.	
Synopsis Other Efficacy Analyses, Pharmacodynamic and Biomarker Analyses; 2.2.3 Additional Endpoints; 9.3.7 Medical Resource Utilization; 11.2 Sample Size Determination; 11.7 Pharmacodynamic and Biomarker Analyses; 16.2.4. Privacy of Personal Data; 17.11. Use of Information and Publication	(*Deleted text is struck-through)* **Pharmacodynamic and Biomarker Analyses** ~~Exploratory~~ Biomarker analyses may be performed, including serum analysis for levels of interferon (IFN) as well as molecular pathway profiling for evidence of IL-12 and IL-23 pathway modulation. The biomarkers analyzed may include inflammatory markers, RNA, auto-antibodies, T, B, and NK cell immunophenotyping, and other categories of biomarkers potentially involved in the development and the progression of SLE. Biomarker results ~~are considered exploratory and~~ will be summarized in a separate technical report. Genetic (DNA) analyses will be conducted only in subjects who sign the optional DNA consent form. These analyses ~~are considered exploratory and~~ will be summarized in a separate technical report.
Rationale: Revised description of biomarker endpoints to clarify that the analyses would be performed on subjects with abnormal levels of that serologic marker at baseline.	
2.2.3 Additional Endpoints	(New text is in bold and underlined) **Disease-specific Clinical Biomarkers** • The change from baseline in serological activity (eg, levels of anti-dsDNA, and other autoantibodies, C3 and C4 levels) over time **in subjects with abnormal levels of that serologic marker at baseline** • The proportions of subjects with normalization, improvement of anti-dsDNA autoantibodies, C3, C4 levels over time **in subjects with abnormal levels of that serologic marker at baseline**
Rationale: Text was revised to include specific mention of SAEs involving medical device incidents.	
12.1.1 Adverse Event Definitions and Classifications, Serious Adverse Events	(N*ew text is in bold and underlined)* • **Results in serious injury/death possibly caused by device malfunction** • **Results in medical or surgical intervention to prevent permanent impairment or damage caused by device malfunction.**

Applicable Section(s)	Description of Change(s)
Rationale: Text concerning missing data was revised in response to the change in randomization methodology.	
Synopsis Missing Data; 11.4.4 Handling Missing Data	(*Deleted text is struck-through and new text is in bold and underlined)* For the primary endpoint, subjects with missing data or meeting treatment failure criteria will be imputed as nonresponders. Sensitivity analyses will be performed and include (1) considering primary endpoint data for subjects meeting treatment failure criteria as missing and (2) using observed data regardless of whether the subject met treatment failure criteria. In both sensitivity analyses, missing response will be imputed by multiple imputation methods **(eg, serial logistic regression)** under the assumption of missing at random. **Additional analyses using observed data without imputation may also be performed**~~If the missing data are not monotone, a Markov chain Monte Carlo method will be used first to effectively make the missing pattern monotone. For monotone missing data, a serial logistic regression method will be used.~~ ********** For all other endpoints, observations after meeting treatment failure criteria will be set to missing for subjects who met the criteria. For binary endpoints, missing data will be imputed using multiple imputation methods **(eg, serial logistic regression) under the assumption of missing at random.** ~~If the missing data are not monotone, a Markov chain Monte Carlo method will be used first to effectively make the missing pattern monotone. For monotone missing data, a serial logistic regression method will be used.~~ For continuous endpoints, the statistical model (ie, MMRM) will adjust for missing data.
Rationale: Corrections were made to indicate that subject diary cards are issued at Week 0 and not throughout the double-blind period and text was revised to clarify that AEs were not to be recorded in subject diaries.	
Section 12	(*Deleted text is struck-through)* ***Solicited Adverse Events*** Solicited adverse events are predefined local and systemic events for which the subject is questioned specifically ~~and which are noted by subjects in their diary~~ (see Section 9.1.1, Overview) ***Unsolicited Adverse Events*** Unsolicited adverse events are all adverse events for which the subject is not questioned specifically ~~in the subject diary~~.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

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

Ustekinumab (STELARA®) is a fully human monoclonal antibody that binds to the p40 protein subunit of human interleukin (IL)-12 and IL-23 cytokines with high affinity and specificity. The binding of ustekinumab to the IL-12/IL-23p40 subunit blocks the binding of IL-12 or IL-23 to the IL-12Rβ1 receptor on the surface of natural killer (NK) and clusters of differentiation (CD)4+ T cells. This inhibits the IL-12 and IL-23 specific intracellular signaling and subsequent cytokine activation and production.

OBJECTIVES, ENDPOINTS, AND HYPOTHESES

Objectives

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.

The secondary objectives are to evaluate the following in subjects with active SLE despite receiving one or more standard-of-care treatments:

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

The additional objectives are to evaluate:

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

Endpoints

The primary endpoint is the proportion of subjects achieving an SLE Responder Index (SRI-4) composite response at Week 52.

The secondary endpoints are:

1. Time to 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 British Isles Lupus Assessment Group (BILAG) A or 2 or more new BILAG B domain scores
2. The proportion of subjects with an 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 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

5. The proportion of subjects achieving at least a 50% improvement in the Cutaneous Lupus Erythematosus Disease Area and Severity Index (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 an SRI-4 composite response at Week 52.

Hypothesis

Treatment with ustekinumab is superior to placebo in subjects with active SLE despite receiving one or more standard-of-care treatments as measured by the proportion of subjects achieving an SRI-4 composite response at Week 52.

OVERVIEW OF STUDY 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 despite receiving 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 (see Section 6 for further details of study agent administration):

- Week 0: Body weight-range based intravenous (IV) administration of ustekinumab (~6 mg/kg) or placebo
- Week 8 and every 8 weeks (q8w) thereafter through Week 48: subcutaneous (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 baseline SLE medications and Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score (a combined factor), using permuted block central randomization.

Clinical and laboratory evidence of disease activity will be evaluated and adjudicated by blinded external reviewers to verify that subjects are meeting inclusion/exclusion criteria and to ensure data quality throughout the study.

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. 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 104, 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 carried out 24 weeks after approximately 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 (eg, other endpoints, other time points) may also be considered. The details of the futility analysis will be included in the Statistical Analysis Plan (SAP).

SUBJECT POPULATION

The target population for this study is subjects between the ages of 16 and 75 years with active SLE according to Systemic Lupus International Collaborating Clinics (SLICC) criteria SLEDAI-2K score ≥6, despite receiving one or more standard-of-care treatments (eg, immunomodulators, antimalarial drugs, and/or glucocorticoids). The target population will include subjects with disease manifestations primarily affecting the skin and joints (most commonly observed disease manifestations in SLE), mucosal ulcers, renal, hematologic, or other disease features. In addition, subjects must have at least 1 positive autoantibody test (antinuclear antibodies [ANA], anti-double-stranded deoxyribonucleic acid (anti-dsDNA) antibodies, and/or anti-Smith antibodies) observed during screening, as well as a well-documented positive autoantibody test in their medical history. Subjects must also have at least 1 BILAG A and/or 2 BILAG B domain scores observed during screening. Additionally, subjects must have a CLASI activity score of at least 4 (excluding diffuse non-inflammatory alopecia) or at least 4 joints with pain and signs of inflammation (active joints) at screening or at Week 0, or both. In addition, subjects must have a clinical SLEDAI-2K score (excluding laboratory results and lupus headache) ≥4 at Week 0, prior to first administration of study agent.

DOSAGE AND ADMINISTRATION

Following randomization at Week 0, subjects assigned to the active treatment 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 the comparable 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 ustekinumab 90 mg SC q8w through Week 160.

For the double-blind study period, subjects will be administered 90 mg ustekinumab or placebo SC q8w at the study site. During the extension period beginning at Week 56 and continuing to Week 160 (and after appropriate and documented training), subjects will be encouraged to self-administer study agent at home.

DESCRIPTION OF STUDY AGENTS

Intravenous Administration

The ustekinumab supplied for this study is a single-use, sterile solution in 30 mL vials with 1 dose strength (ie, 130 mg in 26 mL nominal volume). In addition to ustekinumab, the solution contains 10 mM L-histidine, 8.5% (w/v) sucrose, 0.04% (w/v) polysorbate 80, 0.4 mg/mL L-methionine, and 20 µg/mL ethylenediaminetetraacetic acid (EDTA) disodium salt dihydrate at pH 6.0. No preservatives are present. Placebo study agent will have the same appearance as the respective ustekinumab agent. Except for ustekinumab, the placebo solution contains the same components as active drug.

Subcutaneous Administration

Ustekinumab will also be supplied as a single-use prefilled syringe (PFS) in a strength of 90 mg in 1 mL nominal volume for SC administration. Each 1 mL of ustekinumab solution in the PFS contains 90 mg ustekinumab with nominal excipient concentrations of 6.7 mM L histidine, 7.6% (w/v) sucrose, 0.004% (w/v) polysorbate 80, at pH 6.0. No preservatives are present. The needle cover on the PFS contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex. Except for ustekinumab, the placebo solution contains the same components as active drug.

EFFICACY EVALUATIONS

Efficacy will be evaluated by assessing the following:

- Flares – using BILAG flare and the Modified Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) Flare Index (mSFI) definitions
- Measures of global disease activity – SRI composite response, SLEDAI-2K, Physician's Global Assessment of Disease Activity (PGA), BILAG, Lupus Foundation of America Rapid Evaluation of Activity in Lupus (LFA-REAL) Clinician-reported Outcome (ClinRO) score*
- Glucocorticoid-sparing effects
- Musculoskeletal disease – active, tender, and swollen joint count assessments
- Mucocutaneous disease – CLASI Activity Score
- Assessment of organ domain activity and damage – BILAG and SLEDAI-2K organ domains, CLASI Damage Score,* Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index*
- Low disease activity and remission – SLEDAI-2K score,* BILAG score,* Lupus Low Disease Activity State (LLDAS), Definitions of Remission in SLE (DORIS)*
- Patient-reported outcomes (PROs) – Functional Assessment of Chronic Illness Therapy - Pain visual analogue scale (VAS),* Fatigue (Functional Assessment of Chronic Illness Therapy [FACIT]-Fatigue), 36-Item Short Form Health Survey (SF-36v2; physical component score [PCS], mental component score [MCS], both PCS and MCS, individual domains), EuroQol 5-dimensional, 5-level questionnaire (EQ-5D-5L) index score and VAS score,* Lupus Quality of Life (LupusQoL) domain scores,* Work Productivity and Activity Impairment Questionnaire–Lupus (WPAI-Lupus) total and domain scores, LFA-REAL PRO score*
- Health economics and outcomes research – frequency of hospitalizations,* emergency/urgent care visits,* or unscheduled study visits*

*Results of these exploratory assessments will be summarized in a separate report.

PHARMACOKINETIC and IMMUNOGENICITY EVALUATIONS

- Summary of ustekinumab concentrations and immunogenicity
- Pharmacokinetics (PK)-efficacy relationships for primary and selected key secondary endpoints
- If data allow, population PK and population PK-pharmacodynamics (PD) analysis on primary and/or selected key secondary efficacy endpoints

SAFETY EVALUATIONS

Safety evaluations will include assessment of adverse events (AEs), concomitant medications, pregnancy testing, administration reactions, chemistry, coagulation, hematology, and urinalysis laboratory tests, immunogenicity, vital signs, and general physical examination. In addition, electrocardiogram (ECG), chest x-ray (consistent with local regulations), human immunodeficiency virus (HIV), hepatitis B, hepatitis C, and tuberculosis (TB) testing will be required at screening.

STATISTICAL METHODS

Descriptive statistics (eg, mean, median, standard deviation, interquartile range, minimum, maximum) will be used to summarize continuous variables. Numbers and percentages will be used to summarize categorical variables. Median values will be reported for time to event variables. In addition, graphical data displays (eg, line plots) and subject listings may also be used to summarize/present the data.

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

In general, all statistical tests will be performed at a 2-sided significance level of α=0.05.

Sample Size

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 CNTO1275SLE2001. Additional considerations for powering the study include: (1) increasing the ability to have adequate numbers of subjects for subgroup analyses and (2) maintaining appropriate safety exposure in a pivotal study design.

Primary Efficacy Analyses

Analyses of the primary efficacy endpoint (SRI-4 composite response at Week 52) will include data from all randomized subjects who received at least 1 dose of study agent based on their assigned treatment group regardless of the actual treatment received. The primary analysis will be based upon the composite estimand where subjects meeting treatment failure criteria are assumed to be nonresponders from the point of treatment failure forward, and missing data are assumed as nonresponse.

The SRI-4 composite 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 PGA. Subjects who meet 1 or more treatment failure criteria prior to Week 52 will be considered SRI-4 nonresponders at Week 52 regardless of the observed SRI-4 response status.

Logistic regression, adjusting for baseline stratification factors, region, and baseline SLEDAI-2K, will be used to analyze the primary endpoint. The logistic regression model will include treatment group and stratification factors. The baseline SLEDAI-2K value will be defined as the closest nonmissing measurement taken prior to the Week 0 infusion.

Secondary Efficacy Analyses

With the order specified above, each of the secondary endpoints will be tested at a 2 sided α level of 0.05 if significance is achieved for the preceding hypothesis. 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.

Other Efficacy Analyses

The consistency of efficacy for SRI-4 composite response at Week 52 may be examined in subgroups defined by age, race, baseline SLE Medications and SLEDAI-2K (combined) Score, baseline lupus nephritis, weight, body mass index, and region. Other planned analyses include analysis of additional endpoints.

Missing Data

For the primary endpoint, subjects with missing data or meeting treatment failure criteria will be imputed as nonresponders. Sensitivity analyses will be performed and include (1) considering primary endpoint data for subjects meeting treatment failure criteria as missing and (2) using observed data regardless of whether the subject met treatment failure criteria. In both sensitivity analyses, missing response will be imputed by multiple imputation methods (eg, serial logistic regression) under the assumption of missing at random. Additional analyses using observed data without imputation may also be performed.

For binary major secondary endpoints, analyses will be similar to the analysis of the primary endpoint: subjects with missing data or meeting treatment failure criteria will be imputed as nonresponders. For other secondary endpoints, observations after meeting treatment failure criteria will be set to missing for subjects who met the criteria. No imputation will be performed for missing postbaseline continuous values; the statistical model (ie, mixed-model repeated measures [MMRM]) will adjust for missing data.

For all other endpoints, observations after meeting treatment failure criteria will be set to missing for subjects who met the criteria. For binary endpoints, missing data will be imputed using multiple imputation methods (eg, serial logistic regression) under the assumption of missing at random. For continuous endpoints, the statistical model (ie, MMRM) will adjust for missing data.

Pharmacokinetic Analyses

Serum ustekinumab concentrations will be summarized over time. Descriptive statistics, including arithmetic mean, standard deviation, median, interquartile range, minimum, and maximum will be calculated at each sampling time point. All concentrations below the lowest quantifiable sample concentration of the assay (BQL) or missing data will be labeled as such in the concentration data listing or statistical analysis system (SAS) dataset. The BQL concentrations will be treated as zero in the summary statistics.

Immunogenicity Analyses

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

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

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

Pharmacodynamic and Biomarker Analyses

Biomarker analyses may be performed, including serum analysis for levels of interferon (IFN) as well as molecular pathway profiling for evidence of IL-12 and IL-23 pathway modulation. The biomarkers analyzed may include inflammatory markers, RNA, auto-antibodies, T, B, and NK cell immunophenotyping, and other categories of biomarkers potentially involved in the development and the progression of SLE. Biomarker results will be summarized in a separate technical report.

Genetic (DNA) analyses will be conducted only in subjects who sign the optional DNA consent form. These analyses will be summarized in a separate technical report.

Safety Analyses

Safety analyses will include summaries of discontinuations, deaths, AEs, serious adverse events, and clinical laboratory tests. Targeted safety events in SLE, based on mechanistic plausibility (eg, serious infections, opportunistic infections, TB, hypersensitivity reactions) or potential population risks (eg, worsening of renal or central nervous system [CNS] disease) will also be summarized.

TIME AND EVENTS SCHEDULE: SCREENING PERIOD AND 52-WEEK DOUBLE-BLIND PERIOD

Table 1: TIME AND EVENTS SCHEDULE - Screening Period and 52-Week Double-blind Period

Week	Screening[a] (≤6 Weeks)	Double-blind Period														Follow-up
		0	4	8	12	16	20	24	28	32	36	40	44	48	52	64 *or* EOT[b, c]
Study Procedures[d]																
Screening/Administrative																
Informed consent[e]	X															
Subject assent (if applicable)[f]	X															
Inclusion/exclusion criteria[a]	X	X														
SLE classification by SLICC criteria	X															
Medical history and demographics	X															
Study Agent Administration																
Randomization[g]		X														
Study agent administration (at study site)[h]		X		X		X		X		X		X		X		
Issue subject diary cards		X														
Subject diary cards returned to clinic			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessments																
Full-body physical examination	X	X						X							X	X
Targeted physical examination			X	X	X	X	X		X	X	X	X	X	X		
Electrocardiogram[i]	X															
Chest x-ray[j]	X															
HIV, HBV, and HCV screening	X															
QuantiFERON®-TB test	X															
Tuberculin skin test[k]	X															
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X															
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TB evaluation[l]	X	X		X		X		X		X		X		X		X
Urine pregnancy test[m]	X	X		X		X		X		X		X		X		X

Table 1: TIME AND EVENTS SCHEDULE - Screening Period and 52-Week Double-blind Period																
Week	**Screening[a] (≤6 Weeks)**	**Double-blind Period**														**Follow-up**
		0	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**64 *or* EOT[b, c]**
Review concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Glucocorticoid tapering[n]								← Weeks 24 to 40 →								
Medical resource utilization[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Infusion or injection-site reaction evaluation[p]		X		X		X		X		X		X		X		
Efficacy Assessments[q]																
ClinROs																
BILAG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SLEDAI-2K (S2K RI-50 Baseline and Screening)[r]	X	X														
SLEDAI-2K (S2K RI-50 Follow-up)			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Modified SELENA Flare Index		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physician's Global Assessment of Disease Activity	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Joint count assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CLASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LFA – REAL ClinRO[s]		X			X			X				X			X	
SLICC/ACR Damage Index		X													X	
PROs																
Patient Assessment of Pain Intensity (VAS)		X			X			X				X			X	X
FACIT Fatigue		X			X			X							X	X
SF-36 Standard (4-week recall) v2		X						X							X	
EQ-5D-5L		X						X							X	
LupusQoL		X						X							X	
WPAI-Lupus		X						X							X	
LFA – REAL PRO[s]		X			X			X				X			X	
Medical photography[t]		X			X			X							X	

Table 1: TIME AND EVENTS SCHEDULE - Screening Period and 52-Week Double-blind Period																
Week	**Screening[a] (≤6 Weeks)**	**Double-blind Period**														**Follow-up**
		0	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**64 *or* EOT[b, c]**
Clinical Laboratory Assessments[u]																
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Flow cytometry[v]	X															
Coagulation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C3, C4	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coombs direct test (local lab)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Rheumatoid factor and anti-CCP[g]	X															
Anti-Smith	X															
Antinuclear antibodies	X	X						X							X	X
Anti-dsDNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Other autoantibodies[w]		X						X							X	X
Anti-phospholipid antibodies[x]		X						X							X	X
Ig isotype profile		X						X							X	X
Urine Analyses (spot urine)[u]																
Urinalysis (dipstick, all subjects)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sample for biomarkers (all subjects)	X	X	X		X			X							X	X
Urine protein/creatinine ratio	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sediment analysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics/ Immunogenicity																
Serum ustekinumab concentrations[y]		2X[z]	X	X	X	X	X	X		X		X		X	X	X
Population PK[aa]		← X → (Weeks 0 to 8)			← X → (Weeks 12 to 20)											
Antibodies to study agent[y]		X	X		X			X				X		X		X

Table 1: TIME AND EVENTS SCHEDULE - Screening Period and 52-Week Double-blind Period

Week	Screening[a] (≤6 Weeks)	Double-blind Period														Follow-up
		0	4	8	12	16	20	24	28	32	36	40	44	48	52	64 *or* EOT[b, c]
Biomarkers																
Serum biomarkers	X	X	X		X			X				X			X	X
Whole blood (RNA)	X	X	X		X			X				X			X	X
PBMC (cellular analysis)[bb]	X	X			X			X				X			X	
Whole blood (DNA)[cc]	X															

a. Screening visit must be performed no more than 6 weeks prior to the randomization visit (Week 0). Lupus-specific assessments relating to Inclusion/Exclusion criteria (See Section 4.1) must be reviewed and approved by the Sponsor and/or Sponsor-selected independent reviewer(s) to determine subject eligibility before randomization.

b. It is strongly recommended that subjects who permanently discontinue study agent, but do not withdraw from study participation, be followed at all subsequent study visits through Week 52. At a minimum, subjects who permanently discontinue study agent, but do not withdraw from study participation, should return for a follow-up visit 16 weeks after the last study agent administration to undergo procedures as outlined for the end-of-treatment (EOT) visit. Subjects remaining on study agent and completing the Week 52 visit who do not enter the extension period should return for a follow-up visit 16 weeks after the last study agent administration to undergo Week 64 (EOT visit) procedures.

c. Mandatory at-site visit for subjects who enter the study extension.

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

e. Subjects who are considered to be adults legally (per local requirements) or parents or legal representatives of subjects who are not considered to be adults (per local requirements) will sign informed consent forms for participation in the main study, CNTO1275SLE3001, and may additionally consent for the following: (a) whole blood DNA collection for genetic factors, (b) medical photography at selected sites.

f. Assent for participation in the main study is also required of subjects who are not considered to be adults legally (per local requirements) as described in Section 16.2.3, Informed Consent. Assent may additionally be obtained for the following: (a) whole blood DNA collection for genetic factors, (b) medical photography.

g. At screening, rheumatoid factor and anti-CCP auto-antibodies will be used to assess for co-existing rheumatoid arthritis (RA)/lupus. Before a subject will be approved for randomization, the Investigator must affirm that subjects with positive rheumatoid factor or anti-CCP autoantibodies do not have coexistence of SLE and RA according to the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA.[4]

h. Intravenous administration of study agent at Week 0, all other doses will be subcutaneous (SC) to be administered at the clinic through Week 48.

i. A 12-lead electrocardiogram (ECG) will be performed locally at screening. Subjects should rest in a supine position for at least 5 minutes before ECG recording and should refrain from talking or moving arms or legs.

j. Chest x-ray posterior/anterior and lateral views (or consistent with local regulations) must be taken within 3 months prior to the first administration of study agent for tuberculosis (TB) detection.

k. Only required if QuantiFERON®-TB test is not registered/approved locally or the tuberculin skin test (TST) is mandated by local health authorities.

l. TB evaluation includes an assessment of recent exposure or risk of TB including new or chronic cough, fever, night sweats, unintentional weight loss or recent contact with someone with active TB. If TB is suspected at any time during the study, a chest x-ray (performed locally, consistent with local regulations), and QuantiFERON®-TB test should be performed. A TST is additionally required if the QuantiFERON®-TB test is not registered/approved locally or the TST is mandated by local health authorities. Additional safety procedures may be performed if clinically indicated or mandated by local standards of practice.
m. In addition to the urine screening evaluation, a serum pregnancy test may be conducted at any time at the discretion of Investigator or subject. Urine pregnancy tests may be conducted more frequently (eg, monthly basis) if required by local regulations.
n. See Section 8.1.2 for information on glucocorticoid tapering.
o. Medical resource utilization data (Section 9.3.7), such as hospitalizations, emergency/urgent care visits, or unscheduled visits, will be collected for all subjects throughout the study.
p. Subjects should be monitored for the occurrence of infusion reactions for at least 1 hour after intravenous (IV) infusion and injection-site reactions for at least 30 minutes following SC injection.
q. Whenever possible, patient-reported outcome assessments should be conducted before any tests, procedures, or other consultations for that visit to prevent influencing subjects' perceptions. It is recommended that PROs be performed in the following sequence: Patient Assessment of Pain Intensity (VAS), FACIT-Fatigue, SF-36, EQ-5D-5L, LupusQoL, WPAI-Lupus, and LFA-REAL PRO. It is recommended that ClinRO procedures be performed in the following sequence: BILAG, SLEDAI-2K, mSFI, PGA, joint count assessment, CLASI, LFA-REAL ClinRO, and SLICC/ACR Damage Index. ClinRO assessments should be performed by an adequately trained assessor (see Section 9.2 for details).
r. Complete SLEDAI-2K (baseline) will be evaluated during screening and at Week 0. At Week 0, to be eligible for study participation, subjects must have SLEDAI-2K score ≥4 for clinical features (excluding laboratory results and lupus headache) as assessed by the Investigator.
s. ClinRO portion to be completed by the Investigator at all sites. PRO portion to be performed at selected sites in certain English-speaking countries.
t. Medical photography of skin lesions will be performed at selected sites in subjects with cutaneous disease activity present at baseline who give specific consent.
u. Assessments must be performed by the central laboratory unless otherwise indicated.
v. Perform clinical B-cell flow cytometry analyses at screening for subjects previously exposed to B-cell depleting therapies (such as rituximab and epratuzumab).
w. Other autoantibodies include testing for anti-Smith, anti-Sjögren's-syndrome-related antigen A (SSA anti-Ro) and B (SSB anti-La), anti-ribonucleoprotein (anti-RNP).
x. If an abnormal test result is not obtained at Week 0, no additional follow up testing is required. However, additional testing may be performed if clinically indicated.
y. The same blood draw will be used for the measurement of ustekinumab concentration and detection of antibodies to ustekinumab. For visits with study agent administration, all blood samples for assessing pre-dose ustekinumab concentration and antibodies to ustekinumab **MUST** be collected **BEFORE** the administration of the study agent. Residual sample may be used to evaluate antibodies to ustekinumab at unspecified visits or other biomarker analysis.
z. At Week 0, 2 separate samples for serum ustekinumab concentrations (indicated by "2X" in the Schedule above) will be collected (1 sample will be collected prior to IV infusion and the other collected 1 hour after the end of the infusion) for all subjects.
aa. Additional venous blood sample collection for population PK analysis should occur on any day in each of the 2 designated time periods except on the days of scheduled study visits. Additionally, this blood sample should be collected at least 24 hours prior to or after the actual time of study agent administration.
bb. Whole blood will be collected and processed for peripheral blood mononuclear cell (PBMC) cryopreservation.
cc. Whole blood for genetic analyses will be collected only from subjects who sign a separate informed consent form to participate in the DNA substudy

TIME AND EVENTS SCHEDULE: EXTENSION PERIOD

Table 2: TIME AND EVENTS SCHEDULE – Extension Period (Week 56 Through Week 176)

Week	Extension Period						Follow-up[a]
	56[b]	64[b]	80[b]	112[b]	136[b]	160[b]	176 *or* EOS
Study Procedures[c]							
Study Agent Administration							
Study agent dispensed	X	X	X	X	X	X	
SC study agent administration training[d]	X	X					
Study agent administration[e]	←-- Every 8 weeks SC from Weeks 56-160 --→						
Glucocorticoid tapering	←---------- Per Investigator Discretion ----------→						
Issue subject diaries	X	X	X	X	X	X	
Subject diaries returned		X	X	X	X	X	X
Safety Assessments							
Full-body physical examination	X						X
Targeted physical examination		X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X
TB evaluation[f]	X	X	X	X	X	X	X
Urine pregnancy test[g]	X	X	X	X	X	X	X
Review concomitant therapy	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X
Medical resource utilization[h]	X	X	X	X	X	X	X
Efficacy Assessments[i]							
ClinROs							
BILAG	X	X	X	X	X	X	X
SLEDAI-2K (S2K-RI-50 Follow-up)	X	X	X	X	X	X	X
Physician's Global Assessment of Disease Activity	X	X	X	X	X	X	X
Joint count assessment	X	X	X	X	X	X	X
CLASI	X	X	X	X	X	X	X
SLICC ACR Damage Index				X		X	
PROs							
FACIT-Fatigue				X		X	X
SF-36 Standard (4-week recall) v2				X		X	X
WPAI – Lupus				X		X	

Table 2: TIME AND EVENTS SCHEDULE – Extension Period (Week 56 Through Week 176)

Week	Extension Period						Follow-up[a]
	56[b]	64[b]	80[b]	112[b]	136[b]	160[b]	176 *or* EOS
Study Procedures[c]							
Clinical Laboratory Assessments							
Chemistry	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X
C3, C4	X	X	X	X	X	X	X
Coombs direct test (local lab)	X	X	X	X	X	X	X
Coagulation	X	X	X	X	X	X	X
Anti-dsDNA	X	X	X	X	X	X	X
Ig isotype profile				X			X
Urine Analyses (spot urine)							
Urinalysis (dipstick, all subjects)	X	X	X	X	X	X	X
Urine protein/creatinine ratio	X	X	X	X	X	X	X
Urine sediment analysis	X	X	X	X	X	X	X
Pharmacokinetics/Immunogenicity[j]							
Serum ustekinumab concentrations	X	X	X	X	X	X	X
Antibodies to study agent	X	X	X	X	X	X	X

a. Subjects who complete all scheduled doses or discontinue study agent administration before the end of the study extension should return approximately 16 weeks after last study agent administration to undergo Week 176 (End of Study [EOS] visit) procedures.
b. Mandatory at-site visit for subjects who enter the study extension.
c. All assessments are to be completed prior to study agent administration.
d. Additional visits are permitted for training subjects in study agent self-administration.
e. Following training on study agent administration, study agent may be administered by the subject (or trained designee) at home via SC injection every 8 weeks. Subjects will be required to document administered doses in their subject diaries. Subjects who are unwilling or unable to self-administer study agent at home (eg, because they are following standard practice in their country or because recommended storage conditions are not feasible) are permitted to receive SC injections by a trained designee at the study site or at home.
f. Tuberculosis (TB) evaluation includes an assessment of recent exposure or risk of TB including new or chronic cough, fever, night sweats, unintentional weight loss or recent contact with someone with active TB. If TB is suspected at any time during the study, a chest x-ray (local, consistent with local regulations), and QuantiFERON®-TB test should be performed. A TST is additionally required if the QuantiFERON®-TB test is not registered/approved locally or the TST is mandated by local health authorities.

Table 2: TIME AND EVENTS SCHEDULE – Extension Period (Week 56 Through Week 176)							
Week	**Extension Period**						**Follow-up[a]**
	56[b]	**64[b]**	**80[b]**	**112[b]**	**136[b]**	**160[b]**	**176 *or* EOS**
Study Procedures[c]							

g. A urine or serum pregnancy test may be conducted at any time at the discretion of Investigator or subject, or if required by local regulations.

h. Medical resource utilization data (Section 9.3.7), such as hospitalizations, emergency/urgent care visits, or unscheduled visits, will be collected throughout the study.

i. Whenever possible, patient-reported outcome assessments should be conducted before any tests, procedures, or other consultations for that visit to prevent influencing subjects' perceptions. It is recommended that PROs be performed in the following sequence: FACIT-Fatigue, SF-36, and WPAI-Lupus. It is recommended that ClinRO procedures be performed in the following sequence: BILAG, SLEDAI-2K, PGA, joint count assessment, CLASI, and SLICC/ACR Damage Index. ClinRO assessments should be performed by an adequately trained assessor (see Section 9.2 for details).

j. The same blood draw will be used for the measurement of ustekinumab concentration and detection of antibodies to ustekinumab. All blood samples collected for assessing predose ustekinumab concentration and antibodies to ustekinumab MUST be collected BEFORE the administration of the study agent. Subjects must be instructed to not administer study agent before coming for site visit.

ABBREVIATIONS

ACE	angiotensin-converting enzyme
ACR	American College of Rheumatology
ACTH	adrenocorticotropic hormone
AE	adverse event
ANA	antinuclear antibodies
APS	antiphospholipid syndrome
anti-dsDNA	anti-double-stranded deoxyribonucleic acid
anti-HBc total	HBV core antibody total
anti-HBs	HBV surface antibody
anti-SSA/Ro	anti-Sjögren's-syndrome-related antigen A (also known as anti-Ro)
anti-SSB/La	anti-Sjögren's-syndrome-related antigen B (also known as anti-La)
ARB	angiotensin II receptor blocker
AZA /6 MP	azathioprine/6-mercaptopurine
BAFF	B-cell activating factor, also known as B-lymphocyte stimulator (BLyS)
BCG	Bacille Calmette-Guérin
β-hCG	β-human chorionic gonadotropin
BILAG	British Isles Lupus Assessment Group
BLyS	B-lymphocyte stimulator, also known as B-cell activating factor (BAFF)
CD	clusters of differentiation
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
ClinRO	clinician-reported outcome
CNS	central nervous system
cSFI	classic Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) flare index
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Database lock
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DORIS	definitions of remission in systemic lupus erythematosus
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
ELISA	enzyme-linked immunosorbent assay
EQ-5D-5L	EuroQol 5-dimensional, 5-level questionnaire
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HBsAg	HBV surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
IA	intra-articular
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
Ig	immunoglobulin
IL	interleukin
IM	intramuscular
IP	investigational product
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web response system

LFA-REAL	Lupus Foundation of America Rapid Evaluation of Activity in Lupus
LLDAS	lupus low disease activity state
LupusQoL	Lupus Quality of Life
MCS	mental component score
MMF	mycophenolate mofetil
MMRM	mixed-model repeated measures
MPA	mycophenolic acid
mSFI	modified SELENA flare Index
MTX	methotrexate
NAbs	neutralizing antibodies
NSAIDs	nonsteroidal anti-inflammatory drugs
PBMC	peripheral blood mononuclear cells
PCS	physical component score
PD	pharmacodynamic(s)
PFS	prefilled syringe
PGA	Physician's Global Assessment of Disease Activity
PK	pharmacokinetic
PQC	product quality complaint
PRO	patient-reported outcome
PsA	psoriatic arthritis
q8w	every 8 weeks
RA	rheumatoid arthritis
RNA	ribonucleic acid
RNP	ribonucleoprotein
S2K RI-50	SLEDAI-2K Responder Index
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SF-36	36-Item Short Form Health Survey
SLE	systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SELENA	Safety of Estrogens in Lupus Erythematosus National Assessment
SLICC	Systemic Lupus International Collaborating Clinics
SRI-4	SLE Responder Index
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
Th	T helper
TNFα	tumor necrosis factor alpha
US	United States
VAS	visual analogue scale
WBC	white blood cells
WPAI-Lupus	Work Productivity and Activity Impairment Questionnaire–Lupus

DEFINITIONS OF TERMS

Clinical outcome assessment (COA)	Includes PROs, Clinician-Reported Outcomes (ClinROs), Observer Reported Outcomes (ObsRO) and Performance Reported Outcomes (PerfRO)
Lupus low disease activity state (LLDAS)	Defined as: 1) SLEDAI-2K ≤4, with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever) and no hemolytic anemia or gastrointestinal activity; 2) no new lupus disease activity compared with the previous assessment; 3) a PGA score (scale 0–3) ≤1; 4) a current prednisone (or equivalent) dose ≤7.5 mg daily; and 5) well tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents)

1. INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex, immune-mediated inflammatory disorder of unknown etiology that can affect almost any organ system and follows a waxing and waning disease course. The estimated annual incidence of lupus varies from 1.8 to 7.6 cases per 100,000 people and the worldwide prevalence ranges from 14 to 172 cases per 100,000.[56] It is more prevalent in Afro-Caribbean, Asian, or Hispanic populations and occurs up to 9 times more frequently in women than in men. The highest prevalence of SLE is among women of childbearing age.

In patients with SLE, the immune system attacks the body's cells and tissues and the resulting inflammation and tissue damage can harm the heart, joints, skin, lungs, blood vessels, liver, kidneys, and nervous system. Approximately half of the patients diagnosed with SLE present with organ-threatening disease, but it can take several years to diagnose patients who do not present with organ involvement. Some of the primary complaints of newly diagnosed lupus patients are arthralgia (62%) and cutaneous symptoms (new photosensitivity; 20%), followed by persistent fever and malaise.[56] Patients with mild disease typically have skin rashes and joint pain and require less aggressive treatment. With more severe disease, patients may experience a variety of serious conditions depending on the organ-systems involved, including lupus nephritis with potential renal failure, endocarditis or myocarditis, pneumonitis, pregnancy complications, stroke, and neurological complications, vasculitis, and cytopenias with associated risks of bleeding or infection. Those with severe SLE have a life expectancy that is shortened by 10 to 30 years, largely due to the complications of their disease and/or associated with SLE therapy and accelerated atherosclerosis. The long-term outcome for patients with lupus depends on a variety of factors including whether they have organ involvement, the presence of certain laboratory measures (such as anti-phospholipid antibodies), race, gender, age of onset, access to health care, adherence to treatment, education, and comorbidities. Only about 5% of patients who are diagnosed with SLE will demonstrate a spontaneous remission without treatment.

It is estimated that 10% to 20% of patients experience SLE onset prior to adulthood. The most frequently cited maximum age at diagnosis used to define pediatric-onset SLE is 16 years. Studies that provide direct comparisons of patients with pediatric and adult-onset SLE reveal that pediatric-onset SLE often presents with more acute and severe disease features than adult-onset SLE. Many reports suggest that at the time of diagnosis, there is a higher frequency of renal, neurological, and hematological involvement with pediatric-onset SLE compared with adult-onset SLE. Despite a general lack of comorbid conditions, children and adolescents have higher mortality rates than adults with SLE. Further, a Lupus in Minorities (LUMINA) study showed that there appeared to be more active disease during the disease course in adolescent-onset SLE (SLE onset between age 13 and 18 years) than in those with adult-onset SLE. Almost all children with SLE require treatment with glucocorticoids during the disease course, and many are treated with immunosuppressive agents.[32]

Existing therapies for SLE are generally either cytotoxic or immunomodulatory and may have notable safety risks. Thus, there is a large unmet need for new alternative treatments that can provide significant benefit in this disease without incurring a high safety risk. In the past

fifty years, only one drug with a new mechanism of action has been approved by the European Medicines Agency or the United States (US) Food and Drug Administration (FDA) for treatment of adult SLE. In 2011, the B-lymphocyte stimulator-specific inhibitor belimumab was approved as add-on therapy for the treatment of adult patients with active, autoantibody-positive SLE with a high degree of disease activity despite standard-of-care therapy.[34,54] A variety of new therapeutic agents are being evaluated for the treatment of subjects with refractory lupus; however, to date very few have succeeded in late stage clinical testing or demonstrated notable clinical efficacy beyond those medications currently considered standard of care for patients with this disease.

For the most comprehensive nonclinical and clinical information regarding ustekinumab, refer to the latest version of the Investigator's Brochure[25] and addenda.

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

1.1. Background

To date, ustekinumab has received marketing authorization globally, for the treatment of adult and pediatric patients (age ≥12 to <18 years) with chronic moderate to severe plaque psoriasis, adult patients with active psoriatic arthritis (PsA), and adult patients with moderate to severe Crohn's disease. The cumulative global exposure (through 31 December 2016) has been estimated as 777,478 person-years. Based on completed clinical studies alone, 7,837 subjects have been exposed to ustekinumab across all indications. In Phase 2 and Phase 3 clinical studies, subjects have been exposed to ustekinumab for 6 months, 1 year and some subjects have had 5 or more years of exposure to the drug. The overall safety profile of ustekinumab was similar for patients regardless of indication and the most common adverse reactions (>5%) in controlled periods of clinical studies were nasopharyngitis and headache. Most adverse events (AEs) were considered mild and did not necessitate drug discontinuation. A Phase 2 clinical study of ustekinumab in SLE demonstrated clinical efficacy with no new safety signals compared with previous studies in other indications. The exposure and safety profiles in the SLE Phase 2 study were similar to registrational studies in Crohn's disease using the same dose regimen (Section 1.2.2). Refer to the latest version of the Investigator's Brochure[25] for further details.

1.2. Overall Rationale for the Study

1.2.1. Scientific Rationale for Use of Anti-IL-12/23p40 Therapy in Systemic Lupus Erythematosus

Chronic immune activation in SLE leads to increased production of inflammatory cytokines that contribute actively to local inflammation and to processes that mediate tissue damage. Interferon (IFN) signatures, an increased expression of type I IFN-regulated genes, have been observed to occur more frequently in lupus families and may be a risk factor for development of SLE.[2,35] Several studies have reported an elevation of interleukin (IL)-12, IL-6, and IL-23 in both serum and tissues of patients with SLE, suggesting that the inflammatory environment in SLE is prone to induce T helper (Th)1 and Th17 cells.[7,30,36,42,47,61] Interleukin-12 is produced primarily by

antigen-presenting cells as a secreted heterodimeric cytokine comprising 2 protein subunits, designated p35 and p40 for their approximate molecular weights. In patients with active SLE, messenger ribonucleic acid (RNA) levels of p35 and p40 were significantly higher compared with those in the inactive SLE patients.[23] For clusters of differentiation (CD)4+ T cells, IL-12 signaling concurrent with antigen presentation is thought to invoke differentiation towards the Th1 phenotype, which produces a robust proinflammatory cytokine, interferon gamma (IFNγ). Clear evidence for a genetic link between the IL-23/Th17 pathways in SLE is lacking,[28,44,46] although genome-wide association studies in SLE have identified signal transducer and activator of transcription 4 (STAT4), which mediates Type I IFN, IL-12, and IL-23 signaling, as a susceptibility gene in Asian, Caucasian, and African-American populations.[20,24,45]

Ustekinumab (STELARA®) is a fully human monoclonal antibody that binds to the p40 protein subunit of human IL-12 and IL-23 cytokines with high affinity and specificity. The binding of ustekinumab to the IL-12/IL-23p40 subunit blocks the binding of IL-12 or IL-23 to the IL-12Rβ1 receptor on the surface of natural killer (NK) and CD4+ T cells. This inhibits IL-12- and IL-23-specific intracellular signaling and subsequent cytokine activation and production. This is also supported by preclinical studies implicating IL-12 and IL-23 in animal models and human SLE tissues, limited evidence based on experimental, off-label use of ustekinumab in SLE patients, and its favorable safety profile in several disease indications.

Taken together, these data and investigations from the Alliance for Lupus Research and the Lupus Research Institute, which highlighted ustekinumab as the most prominent drug candidate for repurposing in SLE,[18] strongly support the scientific rationale for further evaluation of the efficacy and safety of ustekinumab in subjects with active SLE.

1.2.2. Results of CNTO1275SLE2001 Phase 2 Study

CNTO1275SLE2001 is a Phase 2, proof-of-concept study of the efficacy and safety of ustekinumab added to standard-of-care background in subjects with active SLE. All subjects in the study were receiving background standard-of-care therapy with glucocorticoids and/or immunomodulators. A total of 102 subjects were randomly assigned to receive either ustekinumab (n=60) or placebo (n=42) through Week 24. Subjects randomized to active drug received an initial body weight-range-based intravenous (IV) dose approximating 6 mg/kg of ustekinumab (ie, 260 mg for subjects ≥35 kg to ≤55 kg; 390 mg for subjects >55 to ≤85 kg; and 520 mg for subjects >85 kg). Subjects randomized to placebo received matching placebo. The IV dose was followed by 90 mg subcutaneous (SC) ustekinumab or matching placebo every 8 weeks (q8w) starting from Week 8. At Week 24, subjects who received placebo crossed-over and all subjects received ustekinumab 90 mg SC q8w without an IV dose. The primary endpoint of the study was the proportion of subjects with a composite measure of SLE disease activity (SRI-4 [SLE Responder Index] composite response) at Week 24.

Subjects were randomized at 36 sites across 5 regions, including Asia Pacific (Taiwan and Australia), Eastern Europe (Hungary and Poland), Western Europe (Spain and Germany), Latin America (Mexico and Argentina), and the US.

All randomized subjects received at least a partial initial IV infusion dose of study agent. Of the 42 subjects in the placebo group and the 60 in the ustekinumab group, 33 subjects in the placebo group and 56 in the ustekinumab group completed their Week 24 visit. Nine subjects in the placebo group and 4 in the ustekinumab group prematurely discontinued study agent.

Efficacy

The primary endpoint of the study was met. At Week 24, a significantly greater proportion of subjects in the ustekinumab treatment group (60.0%; p=0.0046) achieved an SRI-4 composite response than did subjects in the placebo group (31.0%). Sensitivity analyses showed similar treatment effects supporting the robustness of the primary analysis. Ustekinumab also demonstrated greater clinical efficacy versus placebo in measures of SLE disease activity, including systemic features (Systemic Lupus Erythematosus Disease Activity Index 2000 [SLEDAI-2K] and physician's global assessment [PGA]), musculoskeletal disease (active joint counts), mucocutaneous disease (Cutaneous Lupus Erythematosus Disease Area and Severity Index [CLASI]), time to British Isles Lupus Assessment Group (BILAG) flare, and levels of circulating complement C3 and anti-double-stranded deoxyribonucleic acid (anti-dsDNA) autoantibodies.[53]

Safety

The safety analysis set included a total of 102 subjects, with 42 in the placebo group and 60 in the ustekinumab group. Treatment with ustekinumab was generally well tolerated in subjects with SLE, with similar safety profiles observed in the placebo and ustekinumab groups. Through the Week 24 database lock (DBL), no deaths, serious opportunistic infections, active tuberculosis (TB), or malignancies were reported. Key safety results through Week 24 from study CNTO1275SLE2001 are summarized in Table 3. Refer to the current version of the Investigator's Brochure for further details.

Table 3: Overall Summary of Adverse Events Through Week 24; Safety Analysis Set (Study CNTO1275SLE2001)

	Placebo	Ustekinumab
Treated subjects	42	60
Avg duration of follow-up (weeks)	23.3	24.3
Subjects who discontinued study agent because of 1 or more adverse events	4 (44.4%)[a]	3 (75.0%)[a]
Subjects with 1 or more treatment emergent adverse events	28 (66.7%)	47 (78.3%)
Subjects with 1 or more serious treatment emergent adverse events	4 (9.5%)	5 (8.3%)
Deaths	0	0
Subjects with 1 or more infections	21 (50.0%)	26 (43.3%)
Subjects with 1 or more serious infections	0	2 (3.3%)
Subjects with 1 or more malignancies	0	0
Subjects with 1 or more injection-site reactions	0	1 (1.7%)
Subjects with a treatment emergent infusion reaction	1 (2.4%)	2 (3.3%)

a Denominator = number of subjects who discontinued study agent for any reason: 9 in the placebo group and 4 in the ustekinumab group.

Note: Percentage calculated with the number of randomized, treated subjects in each study phase as the denominator. Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

Adapted from: [TSIDS01.RTF] [\\\\\TSIDS01.SAS] 24JUL2017, 09:01; [TSFAE01.RTF] [\\\\\TSFAE01.SAS] 24JUL2017, 09:01; [TSFAE02.RTF] [\\\\\TSFAE02.SAS] 24JUL2017, 09:01[TSFAE05.RTF] [\\\\\TSFAE05.SAS] 26JUL2017, 02:11; [TSFAE06.RTF] [\\\\\TSFAE06.SAS] 26JUL2017, 02:11; [TSFAE09.RTF] [\\\\\TSFAE09.SAS] 26JUL2017, 02:11; [TSFAE08.RTF] [\\\\\TSFAE08.SAS] 26JUL2017, 02:11

Pharmacokinetics

Following a single IV administration of weight-range based ~ 6mg/kg ustekinumab (ie, 260 mg for subjects ≥35 kg to ≤55 kg; 390 mg for subjects >55 to ≤85 kg; and 520 mg for subjects >85 kg) at Week 0, median peak concentration at 1 hour post-dose was 143 µg/mL and median serum concentration at Week 8 was 8.85 µg/mL. Following 90 mg SC q8w administration starting at Week 8, steady state was achieved approximately by Week 24 with a median steady state trough concentration of 2.67 µg/mL. Serum ustekinumab concentrations over time in subjects with SLE were similar to those observed in subjects with Crohn's disease, who received the same dose regimen.[9]

Following the weight-range based IV dose, median serum ustekinumab concentrations were generally similar across the 3 weight categories at the end of Week 8. Following 90 mg SC q8w administration, comparable serum ustekinumab concentrations were generally attained regardless of body weight category through Week 24. The median steady-state trough serum ustekinumab concentrations at Week 24 in subjects with baseline body weight >85 kg (1.49 µg/mL) were slightly lower than in subjects with baseline body weight ≥35 kg to ≤55 kg and >55 kg to ≤85 kg (3.20 and 2.92 µg/mL respectively). However, this did not impact SRI-4 composite response rates in the highest body weight group.

Overall, following treatment with ustekinumab at the dose regimen evaluated in the Phase 2 study, no apparent exposure-response trends were observed between serum ustekinumab concentrations and clinical efficacy measurements. However, these results should be interpreted with caution, given the small number of subjects in each quartile and the relatively narrow drug exposure range following a single-dose regimen of ustekinumab.

Immunogenicity

The overall incidence of antibodies to ustekinumab in the ustekinumab treatment group through Week 24 was 8.5% (5 of 59 subjects with evaluable serum samples). Antibody responses to ustekinumab were generally of low titer; the highest peak titer was ≤1:1600 in one subject. Comparable median serum ustekinumab concentrations were observed between subjects with and without development of antibodies to ustekinumab through Week 24. Thus, development of antidrug antibodies to ustekinumab did not appear to be associated with a reduction in efficacy. However, these results should be interpreted with caution, given the small number of subjects who were positive for antibodies to ustekinumab in the ustekinumab treatment group.

Phase 2 Study Conclusions

- Study CNTO1275SLE2001 has shown that treatment with ustekinumab, administered as an ~6 mg/kg IV dose followed by 90 mg SC at Week 8 and then every 8 weeks thereafter was efficacious and generally well tolerated in subjects with SLE.[53]
- The safety, PK, and anti-drug antibody profile of this dose regimen in the CNTO1275SLE2001 study was consistent with the well-established profile observed in three large-scale Phase 3 Crohn's disease studies using the same dose regimen.[9]

1.2.3. Justification for Dosing Regimen

In the Phase 2 CNTO1275SLE2001 study, greater efficacy compared with placebo was observed across clinical and laboratory measures of disease activity with IV administration of ustekinumab ~6 mg/kg followed by 90 mg SC ustekinumab q8w beginning at Week 8. No new safety signals for ustekinumab administered on a background of standard-of-care therapy were observed in subjects with SLE compared with previous studies in other indications.[25]

The same dosing regimen is proposed for this Phase 3 study of ustekinumab in SLE, and is based on findings from the CNTO1275SLE2001 study as well as the Sponsor's longstanding experience and understanding of the safety and PK-pharmacodynamic (PD) relationships of ustekinumab. PK parameters of ustekinumab have, in general, been similar across multiple indications, including psoriasis, PsA, Crohn's disease, and SLE after correcting for body weight-related PK differences.

Elevation of total circulating IL-12/23p40 has been consistently observed in previous studies of ustekinumab due to the stabilization of p40 by binding of ustekinumab, and has been a reliable measure of target engagement in clinical studies. In the CNTO1275SLE2001 study, the elevated levels of total IL-12/23p40 in SLE subjects observed were similar to those seen in Crohn's disease studies.

Given the multi-organ systemic involvement of SLE, and the high IL-12/23p40 and Th1 cell burden present at baseline in the circulation and tissue, respectively, an IV dose was tested. It was believed that the higher initial exposures enabled by IV administration and the resultant more rapid onset of action, might be important in inducing response and establishing a durable reduction in active signs and symptoms of SLE. In the CNTO1275SLE2001 study, administration of a ~6 mg/kg IV dose of ustekinumab resulted in increased levels of C3 and reduced titers of anti-dsDNA autoantibodies as early as Week 4, suggesting a rapid PD response for clinically relevant markers of disease activity. Further, evidence of a treatment effect of ustekinumab over placebo was observed by Week 12 in most clinical efficacy measures, including SRI-4 composite response.

Most subjects receiving ustekinumab in the CNTO1275SLE2001 study maintained steady-state trough concentrations above 0.8-1.4 µg/mL, an exposure threshold that has been shown to correlate with greater efficacy in subjects with Crohn's disease. Following treatment with SC ustekinumab 90 mg q8w in subjects with SLE, approximately 80% of subjects are predicted to achieve steady‑state trough ustekinumab concentrations ≥1 µg/mL. Given the multi-organ system involvement in SLE, maintenance dosing regimens lower than 90 mg q8w would not be expected to produce optimal efficacy in the SLE population.

Study CNTO1275SLE2001 has shown that treatment with ustekinumab administered as an ~6 mg/kg IV dose following by 90 mg SC dose at Week 8 and then every 8 weeks thereafter was efficacious and generally well tolerated in subjects with SLE.[53] The safety profile of this dose regimen in the CNTO1275SLE2001 study was consistent with the well-established profile observed in several large-scale Phase 3 Crohn's disease studies.[9] Therefore, this dosing regimen was selected for further evaluation in this Phase 3 SLE study.

1.2.4. Benefit/Risk Assessment

To date, ustekinumab has received marketing authorization globally for the treatment of adult and pediatric patients (age ≥12 to <18 years) with chronic moderate to severe plaque psoriasis, adult patients with active PsA, and adult patients with moderate to severe Crohn's disease. The overall safety profile of ustekinumab was similar for patients regardless of indication. Refer to the latest version of the Investigator's Brochure[25] for further details.

Ustekinumab is being evaluated in patients with SLE in a Phase 2 clinical study CNTO1275SLE2001. The results of that study through 24 weeks (see Section 1.2.2) indicate that ustekinumab, administered as an initial body weight-range-based IV dose approximating 6 mg/kg of ustekinumab followed by 90 mg SC ustekinumab every 8 weeks starting from Week 8, is an effective therapy in SLE beyond standard-of-care background therapy. The same dosing regimen is proposed for this Phase 3 study of ustekinumab in SLE.

In the CNTO1275SLE2001 study through the Week 24 DBL, treatment with ustekinumab was generally well tolerated in subjects with SLE, with similar safety profiles observed in the placebo and ustekinumab groups. No deaths, serious opportunistic infections, active TB, or malignancies

were reported. Further, no new safety signals were identified in the SLE study compared with previous studies in other indications.

In this Phase 3 study, potential risks of treatment with ustekinumab (eg, serious infections, including TB and hypersensitivity reactions), as well as the potential risks inherent in patients with SLE (severe disease flares, lupus nephritis, central nervous system [CNS] disease, vasculitis, cytopenias, serious infections, and opportunistic infections), are being addressed in multiple ways:

- Inclusion/exclusion criteria (Section 4.1) set limits regarding, for example, history of unstable or progressive organ-threatening disease, infections or predisposition to infections, history of reactions to biologic agents, and baseline laboratory abnormalities.
- Comprehensive medical monitoring of data by the sponsor during the conduct of this study includes regular assessment of AEs and serious adverse events (SAEs), vital signs, physical examination, and laboratory results (Table 1 and Table 2 Time and Events Schedules) to evaluate individual cases as well as potential emerging safety trends. In addition, as discussed in Section 11.10, an external, independent Data Monitoring Committee (DMC) will provide oversight and will conduct independent evaluation of the safety data accrued in this protocol.
- Certain concomitant medications (Section 8) have been prohibited and limitations set on dose levels of permitted concomitant medications, such as high dose glucocorticoids, cytotoxic agents, and use of multiple biologics simultaneously, that could introduce safety risks due to oversuppression of the immune system.
- Lastly, the steroid-sparing effects of ustekinumab are being evaluated by implementing a glucocorticoid taper from Week 24-40 during the double-blind period and throughout the extension period. This may add benefit by reducing risk of infection and other glucocorticoid-related complications. However, should a subject experience worsening of disease activity, rescue therapy is permitted per medical necessity as outlined in Table 5 and Table 6.

Based on the available safety data in SLE and other disease indications, efficacy data in the SLE Phase 2 study, and proposed safety measures, the overall risk/benefit assessment of ustekinumab in this protocol is acceptable.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives

2.1.1. Primary Objective

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

2.1.2. Secondary Objectives

The secondary objectives are to evaluate the following in subjects with active SLE despite receiving one or more standard-of-care treatments:

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

2.1.3. Additional Objectives

The additional objectives are to evaluate:

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

2.2. Endpoints

Refer to Section 9, Study Evaluations for assessments related to endpoints.

2.2.1. Primary Endpoint

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

2.2.2. Secondary Endpoints

The secondary endpoints are:

1. Time to 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 domain scores
2. The proportion of subjects with an 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 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 9.3.5 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 an SRI-4 composite response at Week 52

2.2.3. Additional Endpoints

Measures of Improvement in Global Disease Activity

- The proportion of subjects with an SRI-4 composite response in the subpopulation who was unable to taper glucocorticoids
- The proportions of subjects with SRI-4, SRI-5, SRI-6, SRI-7, and SRI-8 composite responses over time
- The proportions of subjects with at least a 4-, 5-, 6-, 7-, or 8-point improvement compared with baseline in SLEDAI-2K over time
- The proportions of subjects with at least a 4-, 5-, 6-, 7-, or 8-point improvement compared with baseline in SLEDAI-2K excluding serologic activity (C3, C4, anti-dsDNA autoantibodies) over time
- The proportion of subjects with an SRI-4 composite response at ≥50% of the study visits from baseline to Week 52
- The proportion of subjects with at least a 4-point improvement compared with baseline in S2K RI-50 over time
- The proportion of subjects with no worsening, improvement* in PGA over time
- Lupus Foundation of America Rapid Evaluation of Activity in Lupus (LFA-REAL) clinician-reported outcome (ClinRO)*

Flare

- Annualized flare rate, total number of flares, proportion of subjects with flares, and time to flare analysis of BILAG flares, severe BILAG flares (defined as at least 1 new BILAG A domain score compared with baseline), moderate BILAG flares (defined as at least 2 new BILAG B domain scores compared with baseline)
- Annualized flare rate, total number of flares, proportion of subjects with flares, and time to flare analysis of modified Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) flare Index (mSFI) flares, severe mSFI flares (Section 9.2.4), mild/moderate mSFI flares (Section 9.2.4) compared with baseline

Glucocorticoid Sparing

- The proportion of subjects receiving glucocorticoids at baseline who achieve an average daily glucocorticoid dosage reduction of at least 25% (relative to the baseline dose) to a glucocorticoid dose level ≤7.5 mg/day by Week 40 and sustain that reduction through Week 52
- The proportion of subjects receiving glucocorticoids at baseline who achieve an average daily glucocorticoid dose reduction of at least 50% compared with the baseline dose level by Week 40 and sustain that reduction through Week 52
- The proportion of subjects who require increases in glucocorticoid dose above the baseline dose level over time
- Cumulative average daily glucocorticoid dose over time in subjects receiving glucocorticoids at baseline

Musculoskeletal Disease

- The proportion of subjects achieving at least a 20% or 50% improvement in the number of active joints (defined as joints with pain and signs of inflammation), tender joints (defined as joints with pain on examination), swollen joints (defined as joints with signs of inflammation) over time in subjects with at least 4 active joints at baseline
- Change from baseline in the number of active, tender, swollen joints over time in subjects with at least 4 active joints at baseline

Mucocutaneous Disease

- The proportion of subjects who achieve a 20% or 50% reduction from baseline in CLASI activity score over time in those with a baseline CLASI activity score of at least 4
- The proportion of subjects who achieve a 20% or 50% reduction from baseline in CLASI activity score over time in those with a baseline CLASI activity score of at least 8
- Change from baseline in the CLASI activity score over time in those with a baseline CLASI activity score of at least 4

Assessment of Organ Domain Activity and Damage

- The proportion of subjects with no BILAG worsening compared with baseline over time
- Time to first Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index worsening (defined as SLICC/ACR damage index damage score >0) over time in those subjects with SLICC/ACR damage index score = 0 at baseline*
- Proportion of subjects who remain free of SLICC/ACR damage index progression (defined as SLICC/ACR damage index damage score = 0) over time*
- Proportion of subjects with SLICC/ACR damage index accrual (defined as change from baseline in SLICC/ACR damage index score >0) over time*

Low Disease Activity and Remission

- The proportion of subjects with SLEDAI-2K score of 0, ≤2 over time*
- The proportion of subjects who achieve lupus low disease activity state (LLDAS) over time
- The proportion of subjects with BILAG major clinical response over time*
- The proportion of subjects who achieve clinical remission on treatment according to definitions of remission in SLE (DORIS) over time*

Disease-specific Clinical Biomarkers

- The change from baseline in serological activity (eg, levels of anti-dsDNA and other autoantibodies, C3 and C4 levels) over time in subjects with abnormal levels of that serologic marker at baseline
- The proportions of subjects with normalization, improvement of anti-dsDNA and other autoantibodies, C3, C4 levels over time in subjects with abnormal levels of that serologic marker at baseline*

Patient-reported Outcomes/ Health Economics and Outcomes Research

- Frequency of total and SLE-related hospitalizations, emergency/urgent care visits, or unscheduled visits*
- The proportion of subjects with clinically meaningful improvement in patient-reported outcomes (PROs) over time: pain visual analogue scale (VAS),* Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-Fatigue), 36-Item Short Form Health Survey (SF-36v2; physical component score [PCS], mental component score [MCS], both PCS and MCS, individual domains), Lupus Quality of Life (LupusQoL) domain scores,*
- Change from baseline in PROs over time: EuroQol 5-dimensional, 5-level questionnaire (EQ-5D-5L) index score and VAS score,* Work Productivity and Activity Impairment Questionnaire–Lupus (WPAI-Lupus) total and domain scores, LFA-REAL PRO*
- Proportion of subjects with no worsening (defined as <10% worsening compared with baseline) in Patient's Assessment of Pain VAS over time*

Pharmacokinetics and Immunogenicity

- Summary of ustekinumab concentrations and immunogenicity
- PK-efficacy relationships for primary and selected key secondary endpoints
- If data allow, population PK and population PK-PD analysis on primary and/or selected key secondary efficacy endpoints

Biomarkers

- Predictive biomarkers of treatment response over time

Refer to Section 9 for evaluations and definitions related to study endpoints.

* Results of these exploratory assessments will be summarized in a separate report.

2.3. Hypothesis

Treatment with ustekinumab is superior to placebo in subjects with active SLE despite receiving one or more standard-of-care treatments as measured by the proportion of subjects achieving an SRI-4 composite response at Week 52.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

CNTO1275SLE3001 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, study to evaluate the efficacy, safety, and tolerability of ustekinumab in subjects between 16 (unless restricted by local requirements) and 75 years of age, inclusive, with active, autoantibody-positive SLE despite receiving one or more standard-of-care treatments (ie, immunomodulators, antimalarial drugs, and glucocorticoids; see Section 8). 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.

Unscheduled visits are permitted for cause, such as safety events, worsening SLE disease activity or flare, or to receive SC study agent during the extension period for those subjects who cannot self-administer at home.

Approximately 500 subjects will be randomly assigned in a 3:2 ratio to receive either ustekinumab or placebo with the following treatment administrations (see Section 6 for further details of study agent administration):

- 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 baseline SLE medications and SLEDAI-2K score (a combined factor), using permuted block central randomization. Baseline SLE medications and SLEDAI-2K score will be stratified as follows:

- High dose medications and SLEDAI-2K ≥10
- High dose medications and SLEDAI-2K <10
- Medium dose medications and SLEDAI-2K ≥10
- Medium dose medications and SLEDAI-2K <10

High dose medications are defined as: ≥15 mg/wk methotrexate (MTX), or ≥1.5 mg/kg/day azathioprine/6 mercaptopurine (AZA/6-MP), or ≥1.5 g/day mycophenolate mofetil (MMF)/ ≥1.125 g/day mycophenolic acid (MPA), and/or ≥15 mg/day prednisone or equivalent.

Medium dose medications are defined as: <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 prednisone or equivalent.

Diagnosis of lupus nephritis will be considered valid if based upon the opinion of a nephrologist or rheumatologist who has excluded other potential causes of renal disease. For stratification purposes, presence of lupus nephritis will be defined as clinical evidence that is consistent with lupus nephritis, including one or more of the following:

a. Proteinuria defined as: >0.5 grams protein or greater than 3+ protein by dipstick. A spot urine creatinine/protein ratio > 0.5 can be substituted for the 24-hour protein measurement.

OR

b. The presence of cellular casts on microscopic analysis of spun urine (including red blood cells, hemoglobin, granular, tubular, or mixed casts). Active urinary sediment (>5 red blood cells/high-power field [RBC/hpf]) in the absence of menstruation or infection, or >5 white blood cells [WBC]/hpf in the absence of infection, or cellular casts limited to RBC or WBC casts) can be substituted for cellular casts.

OR

c. Histologic evidence compatible with lupus nephritis on renal biopsy demonstrating immune complex-mediated glomerulonephritis as defined by International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) 2003 Classification Criteria as follows:

- Class I – Minimal mesangial lupus nephritis
- Class II – Mesangial proliferative lupus nephritis
- Class III – Focal lupus nephritis (active and chronic; proliferative and sclerosing)
- Class IV – Diffuse lupus nephritis (active and chronic; proliferative and sclerosing; segmental and global)
- Class V – Membranous lupus nephritis
- Class VI – Advanced sclerosing lupus nephritis

Clinical and laboratory evidence of disease activity will be evaluated and adjudicated by blinded external reviewers to verify that subjects are meeting inclusion/exclusion criteria and to ensure data quality throughout the study.

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 (see Section 9.1.4) may enter the extension period.

Every reasonable effort should be made to keep concomitant medications stable as defined in the protocol (see Section 3.2.4 for information on glucocorticoid tapering). Beginning at the screening visit, all concomitant therapies and all changes in concomitant therapies should be recorded throughout the study.

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

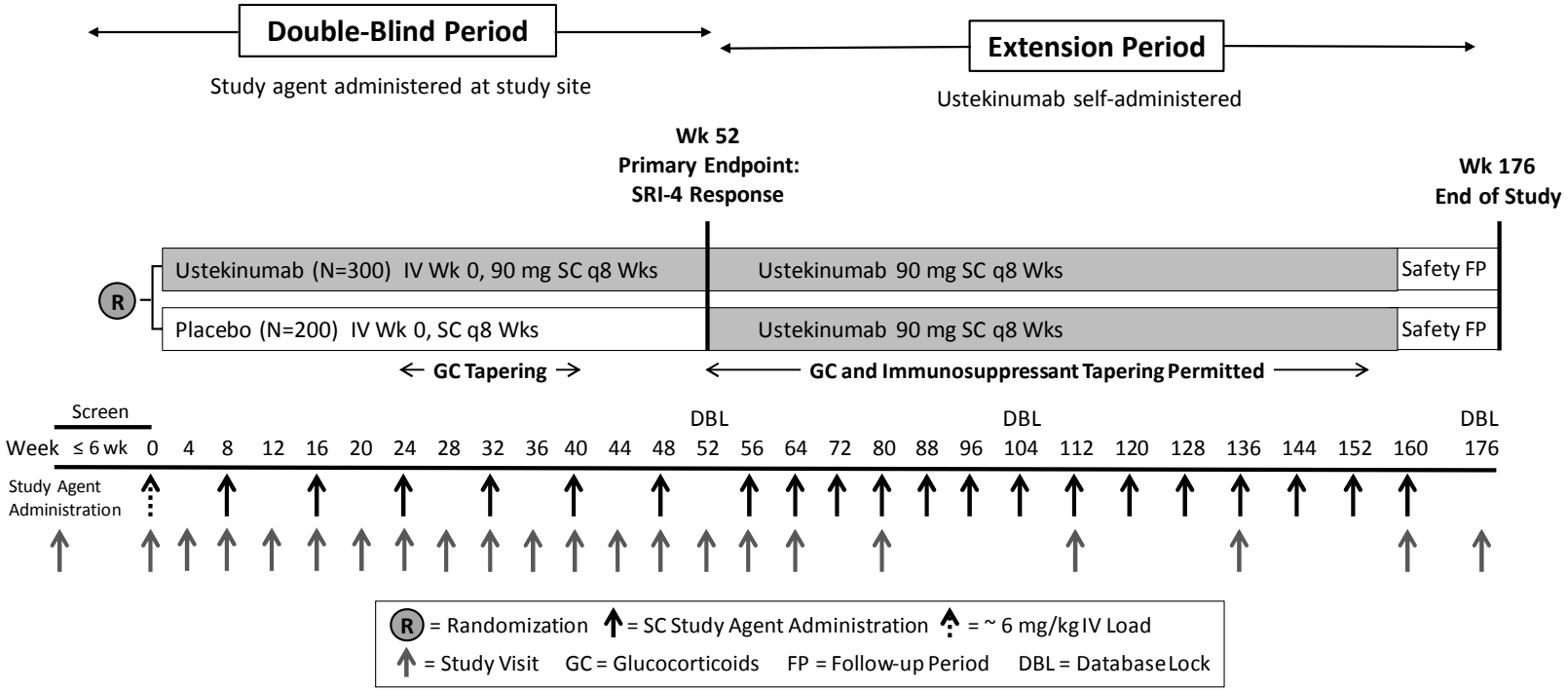
Database locks are planned at Week 52, Week 104, and at Week 176. The end of the study is defined as the last follow-up assessment (16 weeks after the last dose of study agent is administered at Week 160) for the last subject.

An external, independent DMC will be commissioned for this study. Refer to Section 11.11 for further details.

A futility analysis will be carried out 24 weeks after approximately 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 (eg, other endpoints, other time points) may also be considered. The details of the futility analysis will be included in the Statistical Analysis Plan (SAP).

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

Figure 1: Schematic Overview of the Study



3.2. Study Design Rationale

3.2.1. Study Population

The target population for this study is subjects between the ages of 16 and 75 years with active SLE according to SLICC criteria SLEDAI-2K[13] score ≥6, despite receiving one or more standard-of-care treatments (eg, immunomodulators, antimalarial drugs, and/or glucocorticoids).

The target population will include subjects with disease manifestations primarily affecting the skin and joints (most commonly observed disease manifestations in SLE), mucosal ulcers, renal, hematologic, or other disease features. Subjects with less common disease manifestations such as nonprogressive and stable, renal and neuropsychiatric disease will also be permitted to enroll. In addition, subjects must have at least 1 positive autoantibody test (antinuclear antibodies [ANA], anti-dsDNA antibodies, and/or anti-Smith antibodies) observed during screening, as well as a well-documented positive autoantibody test in their medical history. Subjects must also have at least 1 BILAG A and/or 2 BILAG B domain scores observed during screening. Additionally, subjects must have a CLASI activity score of at least 4 (excluding diffuse non-inflammatory alopecia) or at least 4 joints with pain and signs of inflammation (active joints) at screening, or at Week 0, or both. In addition, subjects must have a clinical SLEDAI-2K score (excluding laboratory results and lupus headache) ≥4 at Week 0, prior to first administration of study agent.

Adolescent subjects 16 to <18 years of age will be permitted to enroll. Within the adolescent SLE disease population, there is a large unmet need for new, alternative treatments that can provide significant benefit without incurring a high safety risk. Adolescent SLE subjects will therefore undergo study assessments similar to those for the adult study population since they are generally "adult-like" in their clinical presentation and treatment paradigm. One notable exception is that both parental (or legal representative) consent and subject assent will be obtained in subjects who are not considered to be adults (per local requirements) (Section 4.1.1). Of note, ustekinumab has been evaluated in the pediatric population for various indications (a total of 110 subjects ≥12 to <18 years old). Ustekinumab was safe and well tolerated in this population, which had exposure similar to the adult population, and the safety profile was similar to that seen in studies in adults. Ustekinumab has been approved by the US FDA for the treatment of adolescent patients with moderately to severely active plaque psoriasis (CADMUS study).

The safety and efficacy of ustekinumab has also been evaluated in 310 subjects who were 65 years or older. No major age-related differences in ustekinumab PK were observed in clinical studies that included geriatric subjects. In addition, no differences in safety or efficacy were observed between subjects older than 65 years and those younger than 65 years.[25] However, subjects older than 75 years are excluded because the benefit/risk ratio is less favorable in this population: serious infections, including sepsis, are a major cause of morbidity and mortality in older SLE patients[17,48] and, in many older SLE patients, symptoms are related to the accumulation of chronic damage rather than active disease, which has often resolved.[17]

The incidence and prevalence of SLE varies globally and in certain subpopulations (eg, Asians, those of African descent, and Hispanics are disproportionately affected by the disease compared with those of European descent).[27] In addition, treatment response to certain background medications and potentially investigational agents may differ between different racial and ethnic groups. Thus, this study will investigate the safety and efficacy of ustekinumab in a racially and ethnically diverse population with SLE. In order to evaluate the safety and efficacy of ustekinumab in a broad study population, the target population will include subjects from across the globe (eg, Asia-Pacific region, North America, Europe, Latin America).

3.2.2. Blinding, Control, Study Phase/Periods, Treatment Groups

Treatment groups are outlined in Section 3.1. A placebo comparator (in addition to standard-of-care background therapy) will be used in a 52-week, placebo-controlled period in order to comply with health authority guidance regarding appropriate testing of new compounds in the treatment of SLE, as well as to allow for controlled evaluation of long-term endpoints such as sustained response, disease flares, evaluation of organ systems that may take longer to manifest change, and measures of low disease activity and remission, and reductions in glucocorticoid dose (see Sections 3.2.4 and 8.1.2 for guidelines on glucocorticoid tapering).

Permuted block allocation will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline disease characteristics; Section 5.1) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Blinded treatment through Week 52, will be used to reduce potential bias during data collection and evaluation of clinical endpoints. See Section 5 for further details on randomization and blinding.

3.2.3. Biomarker Collection

Biomarker samples will be collected at selected sites to evaluate the mechanism of action of ustekinumab to help explain interindividual variability in clinical outcomes, or to help identify population subgroups that respond differently to ustekinumab. The biomarker analyses will also evaluate the PD of ustekinumab in SLE and will aid in evaluating the drug-clinical response relationship.

Biomarker samples may be used to enable the development of safer, more effective, and ultimately individualized therapies for SLE.

3.2.4. Glucocorticoid Tapering

Gradual tapering of oral glucocorticoid dosing after Week 24 and through Week 40 will be used to evaluate the steroid-sparing potential of ustekinumab. Stabilizing the glucocorticoid dose between Weeks 40 and 52 will allow evaluation of maintained reductions in glucocorticoid therapy on SLE disease activity (see Section 8.1.2, Glucocorticoid Therapy).

3.2.5. Patient-Reported Outcomes

Patient-reported outcomes on pain, fatigue, lupus disease-specific and general health-related quality of life, and work productivity (WPAI) will be assessed. In addition, evaluation of a subset of subjects using a novel VAS-based assessment tool (LFA-REAL; Section 9.2.13) is planned.

4. SUBJECT POPULATION

Screening for eligible subjects must be performed no more than 6 weeks prior to the randomization visit (Week 0). Approximately 500 subjects with disease manifestations primarily involving the skin and joints who may also have renal, hematologic or other disease features will be enrolled.

The inclusion and exclusion criteria for enrolling subjects in this study are described in Sections 4.1.1 and 4.1.2, respectively. If there is a question about the inclusion or exclusion criteria below, the Investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

4.1. Main Study

4.1.1. Inclusion Criteria

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

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

2. Subjects who are considered to be adults legally (per local requirements) must sign an informed consent form (ICF) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study. Subjects who are not considered to be adults legally (per local requirements) must have parent(s) (preferably both if available or as per local requirements) (or their legally acceptable representative) sign an ICF indicating that he or she understands the purpose of, and procedures required for, the study and is willing to allow the child to participate in the study. Assent is also required of children capable of understanding the nature of the study as described in Section 16.2.3, Informed Consent.

3. Be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

4. Be between 16 (unless restricted by local requirements) and 75 years of age, inclusive.

5. Had a diagnosis of SLE made or confirmed by a physician (such as a rheumatologist, nephrologist, internal medicine specialist, or dermatologist) experienced in the treatment of SLE.

6. Criterion modified per Amendment 2:

6.1 Had a documented medical history (ie, met at least 1 of the bulleted criteria below) that subject met the SLICC classification criteria for SLE[41] at least 3 months prior to first dose of study agent:

- Met a total of at least 4 SLICC criteria, including at least 1 clinical and at least 1 immunologic (Attachment 1).
- Had a diagnosis of lupus nephritis, confirmed by renal biopsy and at least 1 of the following autoantibodies: ANA or anti-dsDNA.

7. Have at least 1 well-documented (subject file, referring physician letter, or laboratory result) unequivocally positive test in medical history for at least 1 of the following autoantibodies: ANA, anti-dsDNA, and/or anti-Smith

8. Have at least 1 unequivocally positive autoantibody test including ANA (≥1:80 titer by Central Lab test) and/or anti-dsDNA antibodies and/or anti-Smith antibodies detected during screening.

9. Have at least 1 BILAG A and/or 2 BILAG B domain scores observed during screening.

10. Have a CLASI activity score of at least 4 (excluding diffuse non-inflammatory alopecia) or at least 4 joints with pain and signs of inflammation (active joints) at screening or at Week 0, or both.

11. Demonstrate active disease based on SLEDAI-2K score ≥6 observed during screening. Must also have SLEDAI-2K ≥4 for clinical features (ie, SLEDAI-2K score excluding headache, and laboratory abnormalities) present at Week 0 prior to randomization.

12. Must be receiving one or more of the following protocol-permitted, systemic standard-of-care treatments:

a) Oral glucocorticoids (average daily dose ≤20 mg of prednisone or equivalent) for ≥6 weeks and at a stable dose ≥4 weeks prior to first dose of study agent

- If currently not using oral glucocorticoids, must not have received them for ≥6 weeks prior to the first dose of study agent.

b) Antimalarials (≤250 mg/day chloroquine, ≤400 mg/day hydroxychloroquine, and/or ≤100 mg/day quinacrine) for ≥12 weeks and at a stable dose for ≥6 weeks prior to first dose of study agent

c) If using one or more of the following immunomodulatory drugs, must be receiving for ≥12 weeks and be on a stable dose for ≥6 weeks prior to first dose of study agent:

- MMF ≤2 g/day

- MPA ≤1.5 g/day
- AZA /6-MP ≤2 mg/kg/day; up to 100 mg/day for subjects weighing ≤50 kg
- Oral MTX ≤25 mg/Week or SC or intramuscular (IM) MTX ≤20 mg/Week with concomitant folic acid or folinic acid

If the subject is using concomitantly 2 or more of the immunomodulatory drugs listed above (MMF, MPA, AZA, 6-MP, MTX), the suitability of the subject to participate in the study must be discussed with the medical monitor and/or sponsor before the subject is randomized.

13. Regular or as needed treatment with the following agents with no changes in dose or frequency is permitted as follows:

a) Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) for ≥2 weeks prior to first dose of study agent

b) Nonsteroidal anti-inflammatory drugs (NSAIDs) or other analgesics for ≥2 weeks prior to first dose of study agent

c) Permitted topical medications for cutaneous disease (Section 8.1.6) for ≥4 weeks prior to first dose of study agent

- Must not be using any prohibited topical medications (such as tacrolimus, pimecrolimus, dapsone, thalidomide), with the exception of cyclosporine A for ophthalmic use

14. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

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

Before randomization, a woman must be either:

a. Not of childbearing potential, defined as:

1) Premenarchal: A premenarchal state is one in which menarche has not yet occurred.

2) Postmenopausal: A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy; however, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

3) Permanently sterile: Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

or

b. Of childbearing potential:

1) Practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: eg, hormone contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomized partner; sexual abstinence (sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study agent. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.

2) Agrees to remain on a highly effective method of contraception throughout the study and for at least 16 weeks after the last dose of study agent.

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

15. A woman of childbearing potential must have a negative urine pregnancy tests (β-human chorionic gonadotropin [β-hCG]) obtained during screening and at Week 0 before the first dose of study agent.

16. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 4 months after receiving the last dose of study agent.

17. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. A man who is sexually active with a woman who is pregnant must use a condom and all men must not donate sperm during the study and for 20 weeks after receiving the last dose of study agent.

18. Are considered eligible according to the following TB screening criteria:

a. Have no history of latent or active TB prior to screening. An exception is made for subjects who have a history of latent TB and are currently receiving treatment for latent TB, will initiate treatment for latent TB prior to first administration of study agent, or have documentation of having completed appropriate treatment for latent TB within 3 years prior to the first administration of study agent. It is the responsibility of the Investigator to verify the adequacy of previous anti-tuberculous treatment and provide appropriate documentation.

b. Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.

c. Have had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB prior to the first administration of study agent.

d. Within 6 weeks prior to the first administration of study agent, has a negative QuantiFERON®-TB test result, or have a newly identified positive QuantiFERON®-TB test result in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated prior to the first administration of study agent. Within 6 weeks prior to the first administration of study agent, a negative tuberculin skin test (Attachment 2), or a newly identified positive tuberculin skin test in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated prior to the first administration of study agent, is additionally required if the QuantiFERON®-TB test is not approved/registered in that country or the tuberculin skin test is mandated by local health authorities.

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

    ii. The QuantiFERON®-TB test and the tuberculin skin test are not required at screening for subjects with a history of latent TB and ongoing treatment for latent TB or documentation of having completed adequate treatment as described above; Subjects with documentation of

having completed adequate treatment as described above are not required to initiate additional treatment for latent TB.

e. Have a chest radiograph, both posterior-anterior and lateral views (consistent with local regulations), taken within 3 months prior to the first administration of study agent and read by a qualified radiologist or pulmonologist, with no evidence of current, active TB or old, inactive TB.

19. Criterion modified per Amendment 2:

19.1 Subjects must have laboratory test results within the following parameters at screening:

Hemoglobin	≥8.0 g/dL	(SI: ≥80 g/L)
Lymphocytes	≥0.5 x 10^3/μL	(SI: ≥0.5 GI/L)
Neutrophils	≥1.0 x 10^3/μL	(SI: ≥1.0 GI/L)
Platelets	≥75 x 10^3/μL	(SI: ≥75 GI/L)
Serum creatinine	≤1.8 mg/dL	(SI: ≤159 μmol/L)

In addition, the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels must be within 3 x the upper limit of normal (ULN) range for the laboratory conducting the test.

A one-time repeat of these screening laboratory tests (eg, hemoglobin, lymphocytes, neutrophils, platelets, serum creatinine, AST, ALT, ANA, anti-dsDNA, anti-Smith) is allowed during the 6-week screening period and the Investigator may consider the subject eligible if the previously exclusionary laboratory test result is within an acceptable range per eligibility criteria on repeat testing at the central laboratory. A screening laboratory test(s) analyzed by the central laboratory may be repeated more than once in the event of suspected error in sample collection or analysis as long as the result is obtained within the 6-week screening period.

Subjects with other marked disease-associated laboratory abnormalities may be included only if the Investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the subject's source documents and initialed by the Investigator. Subjects with Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 laboratory abnormalities must be discussed with the medical monitor and/or sponsor to determine eligibility for enrollment.

4.1.2. Exclusion Criteria

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

1. Criterion modified per Amendment 2

   1.1 Has any unstable or progressive manifestation of SLE (lupus cerebritis, optic neuritis, transverse myelitis, psychosis, uncontrolled seizures, systemic vasculitis, end-stage renal disease, severe or rapidly progressive Class III or IV glomerulonephritis, isolated Class V lupus nephritis [ie, without coexistent Class I, II, III, or IV nephritis], Class VI lupus nephritis, pulmonary hemorrhage, myocarditis) that is likely to warrant escalation in therapy beyond permitted background medications. Subjects requiring renal hemodialysis or peritoneal dialysis are also excluded.

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

3. Is pregnant, nursing, or planning a pregnancy or planning to father a child while enrolled in the study or within 4 months after receiving the last administration of study agent.

4. Is an employee of the Investigator or study site (ie, personnel to whom the Investigator has delegated a role or responsibility for conducting the study), with direct involvement in the proposed study or other studies under the direction of that Investigator or study site, as well as family members of the employees or the Investigator.

5. Lives in an institution on court or authority order, unless permitted by local regulations.

Concomitant or previous medical therapies received:

6. Has received systemic immunomodulatory agents (eg, leflunomide, tacrolimus, sirolimus, mizoribine) other than those described in inclusion criteria within 3 months prior to the first dose of study agent (Section 8.1.7). Glucocorticoids are not included in this criterion; see Section 8.1.2 regarding glucocorticoid use.

7. Has used oral cyclophosphamide within 90 days or IV cyclophosphamide within 180 days of starting screening.

8. Criterion modified per Amendment 2:

   8.1 Exclusions for treatment with B-cell targeted therapies (eg, belimumab, rituximab, epratuzumab)* are as follows:

   a. Treatment with a single B-cell targeted therapy within 3 months prior to first dose of study agent.

   b. Treatment with >1 previous B-cell targeted therapy within 6 months prior to first dose of study agent.

   c. Treatment with B-cell depleting therapy (eg, rituximab, epratuzumab) within 12 months prior to first dose of study agent or have evidence of continued B-cell depletion following such therapy.

   *If a subject has received one or more B-cell targeted therapies, the length of time required before administering the first dose of study agent should be whichever is the longest applicable washout period.

9. Has ever received ustekinumab.

10. Has received prior immunomodulatory biologic therapy not described in Section 8.1.7 such as tocilizumab, alefacept, efalizumab, natalizumab, abatacept, anakinra, brodalumab, secukinumab, ixekizumab, or agents whose mechanism of action targets tumor necrosis factor alpha (TNFα), IL-1, IL-2, IL-6, IL-17, or IFN pathways, less than 5 half-lives or 3 months, whichever is longer, prior to first dose of the study agent.

11. Has received adrenocorticotropic hormone (ACTH) administered by injection within 1 month prior to the first administration of study agent.

12. Criterion modified per Amendment 2:

   12.1 Has received topical cream/ointment preparations of cyclosporine A (except for ophthalmic use), high-potency topical glucocorticoids (World Health Organization [WHO] encoding dictionary), or other topical immunomodulatory agents (such as tacrolimus, pimecrolimus) within 4 weeks prior to the first administration of study agent.

13. Has received an investigational drug that is not previously defined in other exclusion criteria (including investigational vaccines or other medications specified in Section 4.2) within 5 half-lives or 3 months, whichever is longer, or used an invasive investigational medical device within 3 months before the planned first dose of study agent, or is currently enrolled in an interventional study.

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

15. Subjects likely to require multiple courses of systemic steroids (eg, uncontrolled asthma, uncontrolled chronic obstructive pulmonary disease) for reasons other than SLE should be excluded from study participation.

16. Has received epidural, IV, IM, intra-articular (IA), intrabursal, or intralesional administration of glucocorticoids within 6 weeks prior to the first administration of study agent.

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

    NOTE: See also Exclusion 43 and Exclusion 44.

    Infections or predisposition to infections:

18. Has had a Bacille Calmette-Guérin (BCG) vaccination within 12 months of screening.

19. Has received a live virus or live bacterial vaccination within 16 weeks prior to the first administration of study agent.

20. Has a history of active granulomatous infection, including histoplasmosis, or coccidioidomycosis. Refer to Section 4.1 for information regarding eligibility with a history of latent TB.

21. Has a chest radiograph within 3 months prior to the first administration of study agent that shows an abnormality suggestive of a malignancy or current active infection, including TB. Radiographic findings such as pulmonary nodules should be evaluated by an experienced radiologist and/or pulmonologist to determine whether the presentation is suggestive of active infection or malignancy and final assessment documented by the Investigator prior to randomization.

22. Has had a nontuberculous mycobacterial infection or opportunistic infection (eg, cytomegalovirus, pneumocystosis, aspergillosis).

23. Has a history of, or ongoing, chronic or recurrent infectious disease, including but not limited to, chronic renal infection, chronic chest infection (eg, bronchiectasis), chronic infectious sinusitis, recurrent urinary tract infection (eg, recurrent pyelonephritis), an open, draining, or infected skin wound or ulcer.

24. Has a history of human immunodeficiency virus (HIV) antibody positive, or tests positive for HIV at screening.

25. Has a hepatitis B infection. Subjects must undergo screening for hepatitis B virus (HBV; Attachment 4). At a minimum, this includes testing for HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total).

26. Is seropositive for antibodies to hepatitis C virus (HCV), unless has 2 negative HCV RNA test results 6 months apart prior to screening and has a third negative HCV RNA test result at screening.

27. Has experienced a recent single dermatomal herpes zoster eruption within the past 4 months. Has ever had multi-dermatomal herpes zoster (defined as appearance of lesion outside the primary or adjacent dermatome) or CNS zoster infection.

28. Within 2 months prior to first administration of study agent, has had a serious infection (eg, pneumonia, sepsis, or pyelonephritis), or has been hospitalized for an infection, or has been treated with IV antibiotics for an infection. Less serious infections (eg, acute upper respiratory tract infection, simple urinary tract infection) need not be considered exclusionary at the discretion of the Investigator.

Concurrent medical conditions or past medical history and procedures:

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

30. Has inherited complement deficiency or combined variable immunodeficiency.

31. Has urinary protein level of >4 g/day or protein/creatinine ratio estimating >4g/day equivalent proteinuria.

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

33. Has a known hypersensitivity to human immunoglobulin (Ig) proteins (eg, IV Ig).

34. Has known allergies, hypersensitivity, or intolerance to ustekinumab or its excipients (see Section 14.1 and the ustekinumab Investigator's Brochure).

35. Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, immunologic, psychiatric), disease of any organ system, or active acute or chronic infection/infectious illness that, in the Investigator's judgment, will substantially increase the risk to the participant if he or she participates in the study.

36. Has had major surgery, (eg, requiring general anesthesia) within 1 month before screening, or will not have fully recovered from surgery, or has major surgery (eg, requiring general anesthesia) planned during the time the subject is expected to participate in the study or within 1 month after the last dose of study agent administration.

    Note: Subjects with planned minor surgical procedures to be conducted under local anesthesia may participate after discussion with the medical monitor and/or sponsor.

37. Has a transplanted organ (except for a corneal transplant performed >3 months prior to first administration of study agent).

38. Uses semipermanently attached wigs that would interfere with scoring of cutaneous disease.

39. Has or has had a substance abuse (drug or alcohol) problem within the previous 3 years.

40. Is unwilling or unable to undergo multiple venipunctures because of poor tolerability or lack of easy venous access.

    Malignancy or increased potential for malignancy:

41. Presence or history of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin that has been treated with no evidence of recurrence for at least 3 months before the first study agent administration and carcinoma in situ of the cervix that has been documented to be surgically cured).

42. Has a known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy of unusual size or location, clinically significant splenomegaly, or history of monoclonal gammopathy of undetermined significance.

Additional concomitant or previous medical therapies received:

43. Use of IV gamma globulin, apheresis therapy (including but not limited to plasmapheresis, photopheresis, leukocytapheresis), or immunoadsorption is prohibited within 6 months prior to the first administration of study agent and within 4 months after receiving the last administration of study agent.

44. Has ever received stem cell transplantation (including hematopoietic stem cell transplantation and mesenchymal stem cell transplantation).

45. Has undergone a splenectomy.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. A subject's eligibility for study entry, with respect to SLE-related features, will be reviewed by independent medical reviewers in addition to the study sponsor before a subject will be approved for randomization. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study agent is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4 describes the required documentation to support meeting the enrollment criteria. The Sponsor reserves the right to discontinue the subject for any operational or safety reasons.

4.2. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions to be eligible for participation:

1. Refer to Section 8 PRESTUDY AND CONCOMITANT THERAPY for additional details regarding therapies that are prohibited and restricted during the study.

2. Agree to follow all requirements that must be followed during the study as described in the Inclusion and Exclusion Criteria, Sections 4.1 and 4.1.2 (eg, contraceptive requirements).

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

4. Use of additional immunosuppressants or immunomodulators, other than those explicitly allowed in the inclusion/exclusion criteria (Section 4.1 and 4.1.2), are prohibited including but not limited to those listed in Section 8.1.7.

5. Must agree not to receive a live virus or live bacterial vaccination during the study. Subjects must also agree not to receive BCG vaccination for 12 months after last dose of study agent, or any other live vaccine for 16 weeks after receiving the last administration of study agent.

6. Must agree not to receive an investigational medical device or an investigational drug other than study agent for the duration of this study.

7. Skin concealers or topical tan preparations or nonpermanent tattoos should be avoided within 48 hours before a study visit due to their potential to obscure skin disease activity.

8. Subjects should avoid use of any wigs or hair attachments that cannot be readily removed for scalp examination.

5. TREATMENT ALLOCATION AND BLINDING

5.1. Treatment Allocation

Procedures for Randomization and Stratification

Permuted block 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 on 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.

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 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 criteria above for the category of "high" medications would be included in the "medium" medication category.

Based on 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 each subject. A detailed description of the permuted block allocation will be included in the SAP.

5.2. Blinding

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 (eg, study agent serum concentrations, anti-ustekinumab antibodies, 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. (The DMC will review unblinded data and interim analysis results; see Section 11.10 and Section 11.11). At the Week 52 DBL, the data will be unblinded for analysis to some sponsor personnel while subjects are still participating in the study. Identification of sponsor personnel who will have access to the unblinded subject-level data will be documented prior to unblinding. Investigative study sites and subjects will remain blinded to initial treatment assignment until after the final database 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 electronic case report form (eCRF), 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.

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

6. DOSAGE AND ADMINISTRATION

Following randomization at Week 0, subjects assigned to the active treatment 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 the comparable 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. Subjects and Investigators will be aware (open-label) that ustekinumab is the only study agent to

be administered during the extension period. However, subjects and Investigators will remain blinded to initial treatment assignment during the double-blind period for the duration of the study through the final DBL.

During the double-blind study period, subjects will be administered study agent at the study site. Subjects (or their designee) should be trained to administer study agent during the Week 56 and the Week 64 visit of the extension period. Additional training sessions are permitted per Investigator discretion. During the extension period beginning at Week 56 and continuing to Week 160 (and after appropriate and documented training), subjects will be encouraged to administer study agent at home; study agent will be provided to subjects for at-home administration. Subjects who are unwilling or unable to self-administer study agent at home (eg, because they are following standard practice in their country or because recommended storage conditions are not feasible) are permitted to receive SC injections at the study site or at home by a trained designee. See Section 14 for further instructions on the IV and SC administration of the study agent. Additional details may be provided in a pharmacy manual/study site investigational product (IP) and procedures manual that is provided separately (Section 15).

7. TREATMENT COMPLIANCE

Study site personnel will maintain a log of all study agent administered. Drug supplies for each subject will be inventoried and accounted for. Study agent will be administered as an IV infusion by qualified study site personnel and the details of each administration will be recorded in the eCRF (including date, start and stop times of the IV infusion, and volume infused).

During the extension period, if a study visit occurs on the same day that a subject is due to receive his or her next dose, ustekinumab may be administered at the study site. Subjects who are unwilling or unable to self-administer ustekinumab (eg, because they are following standard practice in their country or because recommended storage conditions are not feasible) may return to the study side for additional visits to have study agent administered. Additional visits to the study site should be documented. Subjects will be required to document in their diaries study agent administered at home (see Section 6).

Additional details may be provided in a pharmacy manual/study site IP and procedures manual that is provided separately (Section 15).

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy SLE therapies administered before the screening visit must be recorded at screening. Detailed information of prestudy topical and systemic SLE therapies including dosage and frequency of administration must be recorded. For any therapies that were discontinued, the reason for discontinuation (eg, non-response, loss of response, intolerance, safety concern, etc) should be documented. Modification of an effective preexisting therapy must not be made for the explicit purpose of entering a subject into the study.

Concomitant SLE therapies (and non-SLE concomitant therapies) must be recorded throughout the study beginning at Screening to 16 weeks after the last dose of study agent (any changes

must be recorded throughout the study). Concomitant therapies should also be recorded beyond 16 weeks after the last dose of study agent only in conjunction with new or worsening AEs or SAEs that meet the criteria outlined in Section 12.3.2.

All therapies (such as prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study agent must be recorded in the eCRF. Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and indication.

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

Every reasonable effort should be made to keep concomitant medications stable to avoid introducing non-protocol medications for SLE disease activity through Week 52, or as specified in the following sections. Dose stabilization of all concomitant medications is required prior to randomization (Section 8.1). All medications must meet study protocol guidelines (see Sections 4.1 and 4.1.2, and Table 4 and Table 5, which outline permitted concomitant medication use and dose stabilization requirements prior to randomization and during the blinded study period). It is recommended that all other concomitant medications be maintained at stable doses through the 16-week safety follow-up for those discontinuing the study prematurely, or for those who do not enter the extension period. If necessary, a concomitant medication may be reduced or temporarily discontinued because of abnormal laboratory values, safety and tolerability issues, concurrent illness, or the performance of a surgical procedure, but the change and reason for the medication change should be clearly documented in the subject's medical record. Adjustments in concomitant therapies that do not comply with the study protocol guidelines may cause a subject to be considered a treatment failure for the primary and secondary endpoints through Week 52.

For subjects entering the extension period, concomitant therapy, including glucocorticoids, may be decreased per the Investigator's discretion. Permitted medications and medication adjustments during the extension period are outlined in Section 8.2 and Table 6.

During the entire study, Investigators should consider whether increases in permitted background therapy due to increased SLE disease activity warrant discontinuation of study agent. This should be discussed with the medical monitor and/or sponsor. If protocol-prohibited immunosuppressants (such as cyclosporine or tacrolimus), biologics (such as belimumab or rituximab), cytotoxic agents (such as cyclophosphamide), IV glucocorticoids, or average daily doses of oral glucocorticoids >40 mg (prednisone or equivalent) are initiated for severe, progressive, or unstable SLE disease activity, the subject should be discontinued from the study.

See Section 3.2.4 and Section 8.1.2 for management of glucocorticoid therapy during the blinded treatment period and the extension period.

8.1. Prestudy and Concomitant Medications Through Week 52

Table 4 outlines permitted concomitant medication use and dose stabilization requirements prior to randomization.

Table 4: Permitted Concomitant Medications for SLE, the Minimum Stabilization Period before Randomization, and the Maximum Allowed Doses at Study Randomization

Permitted Concomitant Medications for SLE[a]	Stabilization Period Prior to First Administration of Study Agent	Maximum Allowable Dose
Antimalarials (chloroquine, hydroxychloroquine, or quinacrine)	Treated for ≥12 weeks with stable dosing for ≥6 weeks	≤250 mg/day chloroquine (≤3 mg/kg/day) ≤400 mg/day hydroxychloroquine ≤100 mg/day quinacrine
Oral glucocorticoids	Treated for ≥6 weeks with stable dosing ≥4 weeks before the first dose of study agent. If not currently using oral glucocorticoids, must not have received them or any IV or IM glucocorticoid for ≥6 weeks prior to the first administration of study agent	Equivalent to average daily dose of ≤20 mg prednisone
NSAIDs and other analgesics	At least 2 weeks	No more than the usual marketed doses approved in the country where the study is being conducted
Anti-hypertensive medications (ARBs or ACE inhibitors)	At least 2 weeks	No more than the usual marketed doses approved in the country where the study is being conducted.
Non-biologic immunomodulators:	Treated for ≥12 weeks with stable dosing for ≥6 weeks	
Mycophenolate mofetil (MMF)		≤2 g/day
Mycophenolic acid (MPA)		≤1.5 g/day
Azathioprine (AZA)/ 6-mercaptopurine (6-MP)		≤2 mg/kg/day (up to 100 mg/day for subjects weighing ≤50 kg)
Methotrexate (MTX)[a]		≤25 mg/week, oral; ≤20 mg/Week IM or SC

[a] It is recommended that all subjects taking MTX in this study receive concomitant folate or folinic acid. Subjects receiving concomitant folate or folinic acid should have been treated with stable dosing for ≥6 weeks before the first dose of study agent.

Table 5 summarizes the protocol requirements and any allowed changes in dosing for study-permitted SLE medications during the double-blind study period.

Table 5: Blinded Study Period - Protocol Requirements for Permitted Concomitant SLE Medications

Permitted Concomitant Medications for SLE[a]	**Study Dose at Entry**	**Maximum Allowable Dose During Study**
Antimalarials (chloroquine, hydroxychloroquine, or quinacrine; Section 8.1.1)	≤250 mg/day chloroquine (≤3 mg/kg/day) ≤400 mg/day hydroxychloroquine ≤100 mg/day quinacrine Initiation of new antimalarial treatment is not permitted through Week 52.	
Oral glucocorticoids (Section 8.1.2)[b]	Stable dosing equivalent to average daily dose of ≤20 mg prednisone	**Through Week 6** - Dose adjustment (increase or decrease) of no more than 5 mg prednisone (or equivalent/day) to a maximum average daily dose of 25 mg is allowed **Week 6 through Week 12** - No increases in glucocorticoid dose are permitted. Decreases in glucocorticoid dose of no more than 5 mg prednisone (or equivalent/day) are permitted. Dose reduction to at or below the baseline dose is required in those subjects who increased glucocorticoid dose through Week 6. **Week 12 through Week 24** - no adjustments in glucocorticoid dose are permitted. **Week 24 through Week 40** - glucocorticoid dose reductions not exceeding 10-20% of the current dose per week are strongly encouraged. Reason(s) for not tapering glucocorticoids should be documented. If possible, glucocorticoids should be tapered to an average daily dose of ≤7.5 mg prednisone (or equivalent) or at least a 50% reduction from baseline dose by Week 40 (Section 8.1.2). **Week 40 through Week 52** - no further adjustment of glucocorticoid dose is permitted
NSAIDs and other analgesics (Section 8.1.3)	Stable dosing no more than the usual marketed doses approved in the country where the study is being conducted. Notable changes in NSAID dosing to be recorded in concomitant medications.	
Anti-hypertensive medications (ARBs or ACE inhibitors) (Section 8.1.4)	No more than the usual marketed doses approved in the country where the study is being conducted. Initiation of new ARBs or ACE inhibitors is not permitted through Week 52. Substitution of ACE inhibitors for ARBs or ARBs for ACE inhibitors is permitted if medically necessary.	

Table 5: Blinded Study Period - Protocol Requirements for Permitted Concomitant SLE Medications

Permitted Concomitant Medications for SLE[a]	Study Dose at Entry	Maximum Allowable Dose During Study
Non-biologic immunomodulators (Section 8.1.5):		Stable dosing through Week 52. Initiation of a new immunomodulator is not permitted through Week 52.
Mycophenolate mofetil (MMF)	≤2 g/day	
Mycophenolic acid (MPA)	≤1.5 g/day	
Azathioprine (AZA)/6-mercaptopurine (6-MP)	≤2 mg/kg/day (up to 100 mg/day for subjects weighing ≤50 kg)	
Methotrexate (MTX)[c]	≤25 mg/week (oral) or ≤20 mg/week (IM or SC)	

[a] Permitted concomitant medications are not supplied by the sponsor.
[b] Between Weeks 12 and 52, subjects requiring average daily doses of glucocorticoids for SLE disease activity that exceed their baseline dose at Week 0 will be categorized as treatment failures. While these subjects will be permitted to remain in the study, the Investigator must consider whether glucocorticoid dose increases to an average daily dose ≥40 mg prednisone or equivalent for more than 7 consecutive days or whether a requirement for multiple rescues with glucocorticoid therapy between Weeks 12 and 52 should result in discontinuation of study agent administration.
[c] It is recommended that all subjects taking MTX in this study receive concomitant folate or folinic acid. Guidelines for dose adjustment in the event of MTX toxicity are included in the Trial Center File.

8.1.1. Antimalarial Medications

Stable treatment with hydroxychloroquine, chloroquine, or quinacrine is permitted through Week 52 as shown in Table 4 and Table 5. It is not permitted to introduce or adjust dosing of antimalarials through Week 52; however, if necessary, one antimalarial may be substituted for another. Antimalarials produced by a licensed compounding pharmacy (eg, quinacrine) in the country of administration and using pharmaceutical grade components are allowed. It is recommended that subjects receiving antimalarials receive screening for retinal toxicity according to local guidelines.

8.1.2. Glucocorticoid Therapy

Subjects likely to require multiple courses of glucocorticoids for reasons other than SLE (eg, history of uncontrolled asthma, uncontrolled chronic obstructive pulmonary disease, etc) should be excluded from study participation. However, subjects may receive short courses (2 weeks or less) of oral glucocorticoids for reasons such as prophylactic therapy before surgery (stress-dose glucocorticoids), therapy for certain infections, acute exacerbation of asthma or chronic obstructive pulmonary disease, or other condition (eg, contact dermatitis) not related to increased SLE disease activity. Dosage, duration, and reason for glucocorticoid use in these instances must be documented.

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

Oral Glucocorticoids

If using oral glucocorticoids, subjects must be receiving this medication for at least 6 weeks prior to the first study agent administration and be on a stable dose equivalent to an average daily dose of ≤20 mg prednisone (or equivalent) for at least 4 weeks prior to the first study agent dose.

A summary of allowed glucocorticoid dosing at randomization and any permitted changes during the study are shown in Table 4 and in Table 5 and Table 6, respectively. A suggested gradual glucocorticoid tapering schedule (not exceeding 10%-20% reduction in current average daily dose per week) is recommended. Between Weeks 24 and 40, glucocorticoid tapering is strongly encouraged for all subjects who in the Investigator's judgment have stable or improving disease activity and have not met any criterion for treatment failure (specific details will be provided in the SAP). Reason(s) for not tapering glucocorticoids should be documented.

Glucocorticoid tapering is also strongly encouraged during the extension period between Weeks 52 and 176 (see Section 8.2 and Table 6).

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

- If a subject experiences worsening disease activity while tapering glucocorticoids, further dose decreases may be suspended, and/or their oral glucocorticoid dose may be temporarily increased (ie, glucocorticoid rescue) if deemed necessary by the Investigator.

- Increases in average daily glucocorticoid dose that exceed the baseline dose will result in a subject being considered a treatment failure. If glucocorticoid tapering is interrupted, Investigators are encouraged to resume tapering within 4 weeks.

- Tapering is not recommended if, in the opinion of the Investigator, it would pose a significant risk to the subject.

- It is recommended that subjects be educated about and monitored for symptoms of steroid adrenal insufficiency deficiency (eg, Addisonian symptoms such as fatigue, muscle weakness, decreased appetite, nausea, vomiting, joint and muscle pain) by study staff during periods of steroid tapering, as appropriate.

- While subjects meeting treatment failure criteria for increases in glucocorticoid dose may be permitted to remain in the study, the Investigator must consider whether oral glucocorticoid dose increases to an average daily dose ≥40 mg/day prednisone or equivalent for more than 7 consecutive days or whether a requirement for multiple rescues with glucocorticoid therapy after Week 12 should result in discontinuation of study agent administration and/or potentially require withdrawal from the study.

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

Epidural, IV, IM, IA, intrabursal, or intralesional administration of glucocorticoids is strongly discouraged within 6 weeks prior to the first administration of study agent.

Up to the Week 12 visit, short-term (≤2 weeks) epidural, IV, IM, intrabursal, or intralesional glucocorticoid use should be limited to situations where, in the opinion of the Investigator, there are no adequate alternatives. After Week 12, epidural, IV, IM, intrabursal, or intralesional glucocorticoid use may cause subjects to be considered treatment failures. In addition, it should be noted that subjects will be considered treatment failures if at any time during the study, an IV glucocorticoid dose of >625 mg prednisone equivalent/day for 2 or more days total is administered.

If clinically necessary, a total of 1 or 2 IA injections may be permitted for SLE up to Week 12 and should be recorded as a medical procedure; however, joints treated with IA injections will be imputed as "active" in all subsequent assessments. After Week 12, IA glucocorticoid use may also cause subjects to be considered treatment failures.

ACTH administered by injection is not allowed within 1 month prior to the first administration of study agent and throughout the study.

Rectal Administration

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

Inhalation Glucocorticoids

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

8.1.3. Nonsteroidal Anti-inflammatory Drugs

Prescriptions of NSAIDs and other regularly administered analgesics should not be adjusted for at least 2 weeks prior to the first administration of the study agent and through Week 52, and may be changed only if the subject develops unacceptable side effects. Subjects are permitted to receive the usual marketed doses approved in the country in which the study is being conducted. NSAIDs, including aspirin or selective cyclooxygenase-2 (COX-2) inhibitors, and other analgesics (including topical or injectable NSAIDs, analgesics or other pain-relieving agents

such as capsaicin) that are used on an "as needed" basis should not be used within 48 hours before a study visit.

8.1.4. Anti-hypertensive Medications

Subjects are permitted to receive stable doses of ARB or ACE inhibitors for the treatment of hypertension, cardiovascular disease, kidney disease, and lupus nephritis. If receiving regular treatment with ACE inhibitors or ARBs, subjects must be receiving stable dosing for at least 2 weeks prior to first administration of study agent. If necessary, subjects are permitted to switch between ARB and ACE inhibitors or vice versa. Effort should be made to ensure that the effective doses of the switched drugs are comparable. Subjects should not initiate ARB- or ACE-inhibitor therapy between randomization and Week 52.

8.1.5. Non-biologic Immunomodulators

If receiving immunomodulators, subjects should be receiving stable dosing from screening through Week 52. Subjects can be receiving MMF/MPA, AZA/6-MP, and/or MTX with recommended concomitant folic or folinic acid (Table 5). A reduction in immunomodulators is allowed only if the subject develops unacceptable side effects, with the implication that this may affect interpretation of the subject's clinical data. A higher dose of an immunomodulator (relative to the baseline dose) or the addition of a new immunomodulator to the existing treatment regimen will cause subjects to be considered a treatment failure. Any increase in dose of immunomodulator (relative to baseline) must be discussed with the study sponsor and/or medical monitor to determine whether it may require discontinuation of study agent.

8.1.6. Topical Medications

Regular use of topical medications is permitted. However, topical compounds cannot include a prohibited medication. For example, topical ointments or creams that include cyclosporine A, tacrolimus, pimecrolimus, dapsone, or thalidomide are prohibited through Week 52; however, ophthalmic use of cyclosporine A is permitted. "As needed" use of topical NSAIDs, analgesics, or other pain-relieving agents such as capsaicin is permitted, but not within 48 hours prior to study visit. "As needed" use of topical low (Class VI, VII) to moderate (Class IV, Class V) potency glucocorticoids (according to the World Health Organization classification of topical glucocorticoids) is permitted, but not within 48 hours prior to a study visit. High potency topical glucocorticoids are not allowed through Week 52 for all subjects with cutaneous involvement.

8.1.7. Prohibited Therapies

Use of additional immunosuppressants or immunomodulators, other than those explicitly allowed in the inclusion/exclusion criteria (Section 4.1 and 4.1.2), are prohibited including, but not limited to, the following:

- Agents targeted at reducing TNFα (eg, infliximab, golimumab, certolizumab pegol, etanercept, CT-P13, and adalimumab)

- B-cell targeted agents (anti-CD20 eg, rituximab, anti-B-cell activating factor [BAFF], also known as B lymphocyte stimulator [BLyS], eg, belimumab, or anti-CD22 eg, epratuzumab, or other B-cell targeted therapies, such as tabalumab, atacicept, daratumumab)
- Interleukin-1 inhibitors (eg, canakinumab)
- Interleukin-2 inhibitors or exogenous IL-2 therapy
- Interferon inhibitors or exogenous IFN therapy
- IL-1 receptor antagonist (eg, anakinra)
- Tocilizumab or any other biologic targeting IL-6 or IL-6 receptor
- Tofacitinib or any other janus kinase (JAK) inhibitor
- Abatacept
- Anti-IL-17 agents (eg, brodalumab, secukinumab, and ixekizumab)
- Leflunomide
- Cyclosporine A (oral or topical ointment/cream preparations) except for ophthalmic use
- Tacrolimus or pimecrolimus, or other immunomodulatory oral or topical preparations (see Section 8.1.6)
- Toll-like receptor inhibitors
- Thalidomide or lenalidomide
- Dapsone
- Adrenocorticotropic hormone (ACTH) by injection
- IV glucocorticoids (see Section 4.2)

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

Multiple administrations of high doses of oral glucocorticoids (average daily dose ≥40 mg), or initiation of high potency topical glucocorticoids, are prohibited during the study as defined in Section 8.1.2.

Sulfa-based antibiotics, where reasonable, should generally be avoided.

The use of complementary therapies (eg, herbs, ointments, traditional Chinese medicine, acupuncture) that have the potential to activate or inhibit the immune system is prohibited (see Section 4.1.2). In addition, use of complementary therapies that have the potential to interact with antithrombotic agents is prohibited in those taking antithrombotic agents.

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

8.2. Concomitant Medications Use and Rescue Therapy During the Extension Period

Increases in doses of current medications or addition of new protocol-permitted medications for SLE disease activity, such as NSAIDs, ACE inhibitors, ARBs, immunomodulators (antimalarials, MTX, MMF/MPA, AZA/6-MP) and, potentially, topically applied or locally injected therapies (if clinically indicated) are permitted but should be discussed with the medical monitor and/or sponsor.

Severe, progressive, or unstable worsening of SLE disease activity that requires escalation in therapy, including biologics such as belimumab or rituximab, systemic immunomodulators such as cyclosporine or tacrolimus, sustained high doses of oral glucocorticoids, use of IV glucocorticoids, or use of cytotoxic agents such as cyclophosphamide will require discontinuation from the study (see Section 8).

Glucocorticoid dose reductions not exceeding 10-20% of the current dose per week are strongly recommended during the extension period (Table 6). If possible, glucocorticoids may be completely tapered off by the end of study visit.

Reductions in dose or discontinuation of existing background medications is permitted during the extension period per Investigator discretion. Subjects will be issued diary cards to record use of background SLE medications between study visits. All medication changes during the extension period should be recorded in the concomitant therapy section of the eCRF.

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

Table 6: Extension Period- Protocol Requirements for Permitted Concomitant SLE Medications

Permitted Concomitant Medications for SLE[a]	**Study Dosing at Entry**	**Maximum Allowable Dose During Study**
Antimalarials (chloroquine, hydroxychloroquine or quinacrine) (Section 8.1.1)	≤250 mg/day chloroquine (≤3 mg/kg/day) ≤400 mg/day hydroxychloroquine ≤100 mg/day quinacrine	
Oral glucocorticoids (Section 8.1.2)	Stable dosing equivalent to average daily dose of ≤20 mg prednisone	Glucocorticoid dose reductions not exceeding 10-20% of the current dose per week are recommended. If possible, glucocorticoids may be completely tapered off by the end-of-study visit.
NSAIDs and other analgesics (Section 8.1.3)	No more than the usual marketed doses approved in the country where the study is being conducted. Notable changes in NSAID dosing to be recorded in concomitant medications.	

Table 6: Extension Period- Protocol Requirements for Permitted Concomitant SLE Medications

Permitted Concomitant Medications for SLE[a]	Study Dosing at Entry	Maximum Allowable Dose During Study
Anti-hypertensive medications (ARBs or ACE inhibitors) (Section 8.1.4)	No more than the usual marketed doses approved in the country where the study is being conducted. Substitution of ACE inhibitors for ARBs or ARBs for ACE inhibitors is permitted if medically necessary. Addition of a new ARB or ACE inhibitor may be permitted during the extension period after discussion with the medical monitor and/or sponsor.	
Non-biologic Immunomodulators (Section 8.1.5):		Addition of a new permitted immunomodulator or increases in dose of a current immunomodulator should be discussed with the medical monitor and/or sponsor.
Mycophenolate mofetil (MMF)	≤2 g/day	
Mycophenolic acid (MPA)	≤1.5 g/day	
Azathioprine (AZA)/6-mercaptopurine (6-MP)	≤2 mg/kg/day (up to 100 mg/day for subjects weighing ≤50 kg)	
Methotrexate (MTX)[b]	≤25 mg/Week (oral) or ≤20 mg/Week (IM or SC)	
Topical agents (eg, cyclosporine A, tacrolimus, pimecrolimus) (Section 8.1.6),		Should be discussed with the medical monitor prior to administration, and should be clearly documented
Locally administered therapies (eg, intramuscular, intra-articular, intrabursal, or intralesional glucocorticoids; Section 8.1.2)		Should be discussed with the medical monitor prior to administration, and should be clearly documented

[a] Permitted concomitant medications are not supplied by the sponsor.
[b] It is recommended that all subjects taking MTX in this study receive concomitant folate or folinic acid. Guidelines for dose adjustment in the event of MTX toxicity are included in the Trial Center File.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

Table 1 (TIME AND EVENTS SCHEDULE: Screening Period and 52-Week Treatment Period) and Table 2 (TIME AND EVENTS SCHEDULE: Extension Period) summarize the frequency and timing of measurements and sample collection applicable to this study.

Whenever possible PRO assessments should be conducted/completed before any tests, procedures, or other consultations to prevent influencing subject perceptions. Urine and blood collections for PK and PD assessments should be kept as close to the specified time as possible

and are to be collected prior to study agent administration unless otherwise specified (eg, population PK sample). Other measurements may be done earlier than specified timepoints if needed.

It is recommended that PROs be performed in the following sequence: Patient Assessment of Pain Intensity (VAS), FACIT-Fatigue, SF-36, EQ-5D-5L, LupusQoL, WPAI-Lupus, and LFA-REAL PRO. It is recommended that ClinRO procedures be performed in the following sequence: BILAG, SLEDAI-2K, mSFI, PGA, joint count assessment, CLASI, LFA-REAL ClinRO, and SLICC/ACR Damage Index. ClinRO assessments should be performed by an adequately trained assessor (see Section 9.2 for details).

Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study and

- At 8-week intervals starting at Week 0 through Week 52 and at the end-of-treatment or the end-of-study visit.
- Pregnancy testing will be performed at every visit during the extension period, and additional pregnancy testing may be performed as necessary.
- If experiencing a delayed menstrual period (over 1 month between menstruations) or infrequent or irregular menstrual cycles to confirm absence of pregnancy

Subjects who consent to participate in medical photography, will have photographs of target cutaneous lesions or areas of active disease as noted in Table 1 and Section 9.8.

The total blood volume to be collected from each subject over the course of the double-blind portion of the study through Week 64 follow-up will be approximately 730 mL. The total blood volume to be collected in the extension period from Week 56 to Week 176 will be approximately 140 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1.2. Screening Phase

Written informed consent (and written informed assent for subjects who are not considered to be adults legally per local requirements) must be obtained and reviewed by the Investigator before any screening data are collected.

Screening procedures will be performed as indicated in Table 1. The screening visit must be performed no more than 6 weeks prior to the randomization visit (Week 0).

- Subjects must undergo testing for TB and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. The subject should be asked about past testing for TB, including chest radiograph results and responses to tuberculin skin or other TB testing. Investigators have the option to use both the QuantiFERON®-TB test and the tuberculin skin test (Attachment 2) to screen for latent TB if they believe, based on their judgment, that the use of both tests is clinically indicated in order to evaluate a subject who has high risk of

having latent TB. If either the QuantiFERON®-TB test or the tuberculin skin test is positive, the subject is considered to have latent TB infection for the purposes of eligibility for this study.

Women of childbearing potential must have a negative urine pregnancy test at screening and at Week 0 before randomization. In addition to the urine pregnancy screening evaluation, a serum β-hCG pregnancy test may be conducted at any time at the discretion of Investigator or subject. Women of childbearing potential and men must consent to use highly effective methods of contraception (see Section 4.1) and continue to use contraception for the duration of the study and for 4 months after the last dose of study agent. The method(s) of contraception used by each subject must be documented.

All screening evaluations establishing subject eligibility will be performed and reviewed by the Investigator before a subject can be randomized. Subjects must have received approval for study randomization following review of screening lupus assessments by the sponsor and/or sponsor-selected independent reviewer(s). A data review committee will consist of a team of sponsor and/or sponsor-selected independent reviewer(s) who will evaluate suitability of subjects for randomization based on scoring of clinical assessment tools (eg, SLEDAI-2K, BILAG, joint count assessments, CLASI) performed at screening. Details of the data review process will be provided in a separate manual.

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

9.1.2.1. Retesting/Rescreening

A one-time repeat of screening laboratory tests (eg, hemoglobin, lymphocytes, neutrophils, platelets, serum creatinine, AST, ALT, ANA, anti-dsDNA, anti-Smith) is allowed during the 6-week screening period and the Investigator may consider the subject eligible if the previously exclusionary laboratory test result is within an acceptable range per eligibility criteria on repeat testing at the central laboratory. A screening laboratory test(s) analyzed by the central laboratory may be repeated more than once in the event of suspected error in sample collection or analysis as long as the result is obtained within the 6-week screening period.

The goal of the retest procedure is to assess if the subject is eligible for randomization within the screening window or is a screen failure. Subjects who have laboratory values that do not meet entry criteria following the retest or do not meet disease activity criteria following the repeat procedure are to be deemed screen failures. Exceptions to this are positive QuantiFERON®-TB, hepatitis C or B, or HIV tests; unless there is a suspected error in sample collection or analysis performance, these tests may not be repeated to meet eligibility criteria.

If the investigator wishes to rescreen a subject who has failed screening, the investigator should discuss it with the study sponsor and/or their designee. Only 1 rescreening is allowed per subject.

Subjects who are rescreened will be assigned a new subject number, undergo the informed consent process again, and start a new screening phase.

9.1.3. Double-blind Treatment Phase

9.1.3.1. Day of Randomization

Eligible subjects will be randomly assigned by the IWRS in a 3:2 ratio to receive either ustekinumab or placebo in a blinded manner. Assessments will be performed as indicated in the Time and Events Schedule (Table 1). Subjects will be administered blinded IV study agent. Subjects participating in the cutaneous lupus substudy will have baseline, pretreatment photographs taken.

9.1.3.2. Double-blind, Placebo-controlled Treatment Period

After randomization and the first administration of study agent by IV infusion, subjects will have SC blinded study agent administration 8 weeks after the IV dose and q8w thereafter through the Week 48 visit. Assessments will be performed as indicated in Table 1.

Subjects participating in medical photography will have posttreatment photographs taken at Weeks 12, 24, and 52 (see Section 9.8).

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

"Have you/Has your child had a new cough of > 14 days' duration or a change in a chronic cough?"

"Have you/Has your child had any of the following symptoms:

- Persistent fever?
- Unintentional weight loss?
- Night sweats?"

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

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

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

Subjects who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph, a repeat QuantiFERON® TB test, a repeat tuberculin skin test in countries in which the QuantiFERON®-TB test is not approved/registered or the tuberculin skin test is mandated by local health authorities, and, if possible, referral to a physician specializing in TB to determine the subject's risk of developing active TB and whether treatment for latent TB is warranted. If the QuantiFERON®-TB test result is indeterminate, the test should be repeated as outlined in Section 4.1.1. Subjects should be encouraged to return for all subsequent scheduled study visits according to the protocol.

9.1.4. Extension Period

Subjects will be eligible to participate in the extension period when they have completed participation in the main study through the Week 52 visit; subjects who do not complete the Week 52 visit are not eligible to enter the extension. The purpose of the extension is to evaluate the safety, efficacy, and pharmacologic effects of ustekinumab in SLE for a maximum total duration of approximately 2 years beyond the 52-week main study period. Eligible subjects will enter the extension at Week 56. Any subject who does not enter the extension period should follow the Time and Events schedule for the main study (Table 1), and have a safety follow-up visit conducted 16 weeks after their last dose of study agent.

See Section 8.2 and Table 6 for concomitant medication use and rescue therapy during the extension period. The timing and procedures for the extension period are presented in Table 2.

9.1.4.1. Subject Selection

To be eligible to enter the extension study, subjects must meet the following criteria:

- Have completed the Week 52 visit. Subjects who withdraw consent and/or have permanently discontinued study agent administration prior to the Week 52 visit will be not be eligible to enter the extension period.
- In the judgment of the study Investigator, the potential benefit of continuing long-term treatment with study agent outweighs the potential risks for the subject.

9.1.4.2. Dosing Regimen

Subjects (or their designee) should be trained to administer study agent during the Week 56 and the Week 64 visit of the extension period. Additional training sessions are permitted per Investigator discretion.

Subjects who received ustekinumab 90 mg SC q8w during the double-blind period will continue to do so during the extension period. Subjects who received placebo during the double-blind study period will cross over to receive ustekinumab 90 mg q8w beginning at Week 56. IWRS will be preprogrammed to coordinate the crossover of study agent while maintaining the blind. A safety follow-up visit will occur 16-weeks after the final administration of study agent.

9.1.5. End of Study/Early Withdrawal

Subjects who discontinue study agent or active participation in the study will no longer receive study agent. Subjects who withdraw early from study participation will be required to return for follow-up assessments. When a subject withdraws from the study, the reason(s) for withdrawal, if available, should be recorded by the Investigator on the relevant page of the eCRF. Whenever possible, all subjects who discontinue study agent or withdraw from the study prematurely will undergo all end of study assessments as shown in Table 1 and Table 2.

9.1.6. Posttreatment Phase (Follow-Up)

It is strongly recommended that subjects who permanently discontinue study agent, but do not withdraw from study participation, be followed at all subsequent study visits through Week 52. At a minimum, subjects who permanently discontinue study agent, but do not withdraw from study participation, should return for a follow-up visit 16 weeks after the last study agent administration to undergo procedures as outlined for the end-of-treatment (EOT) visit (Table 1). Subjects remaining on study agent and completing the Week 52 visit who do not enter the extension period should return for a follow-up visit 16 weeks after the last study agent administration to undergo Week 64 (EOT visit) procedures.

Every effort should be made to record the reason for study agent and/or study discontinuation. If the information on reasons for discontinuation is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the subject has died, the date and cause of death will be collected and documented on the eCRF.

Investigators may recontact the subject to obtain long-term follow-up information regarding the subject's safety or survival status as noted in the informed consent form (refer to Section 16.2.3, Informed Consent).

9.2. Efficacy Evaluations

All efficacy evaluations should be performed consistently by the same study Investigator or subinvestigator at every visit to achieve comparable measures over time. It is recommended that the designated assessor identify an appropriate backup in case the designated assessor is unavailable.

ClinROs, including joint assessments, should be performed by an adequately trained assessor, preferably a rheumatologist. If a rheumatologist is not available, the assessor should be a health care provider with at least 1 year of experience in scoring these instruments. A health care provider with less than 1 year of experience may serve as a ClinRO assessor only with the approval of the sponsor. It is recommended that the designated assessor identify an appropriate backup.

Independent data review by the sponsor or sponsor-designated independent reviewer(s) will be performed throughout the study for key SLE assessments (eg, SLEDAI-2K, BILAG, joint count assessments, mSFI, and CLASI). These data will be reviewed at every visit that these data are collected and may require reconciliation of inconsistencies across assessments.

9.2.1. SLE Disease Activity Index 2000

The SLE disease activity index 2000 (SLEDAI-2K) is an established, validated SLE activity index. It is based on the presence of 24 features in 9 organ systems and measures disease activity in SLE patients in the previous 30 days; the index is weighted according to the feature. Features are scored by the assessing physician if present within the last 30 days, with more severe features having higher scores, and then simply added to determine the total SLEDAI-2K score, which ranges from 0 to 105.[50,51] The baseline measurement for the SLEDAI-2K is defined as the closest measurement taken prior to the initiation of the Week 0 study agent administration.

SLEDAI improvement is defined as a reduction from baseline in total SLEDAI-2K score. No worsening of total SLEDAI-2K from baseline is defined as a change ≤0 in SLEDAI-2K score. At baseline, the features assessed in the SLEDAI-2K are used for comparison to the SLEDAI-2K RI-50 [Follow-up] described below.

The SLEDAI-2K has been adapted and developed into the SLEDAI-2K RI-50, a measure that can document partial improvement in the 24 disease features between 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.[49,52]

9.2.2. British Isles Lupus Assessment Group

The BILAG index[21,26] 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.[26] 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.

- **BILAG Improvement** is defined as (1) all BILAG A scores at baseline improved to either B, C or D and (2) all BILAG B scores at baseline improved to C or D and (3) no worsening in disease activity defined as no new BILAG A scores and ≤ 1 new BILAG B score.
- **Major Clinical Response in BILAG** is defined as BILAG C score or better in all organ domains.
- **No worsening in BILAG disease activity** is defined as no new BILAG A scores and ≤1 new BILAG B score.

9.2.3. Physician's Global Assessment of Disease Activity

The PGA[38,39] independent of subjects' assessment is recorded on a 10-cm 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.

- **No worsening in PGA** defined as no significant deterioration (<10% increase from baseline) using a 10-cm visual analogue scale.[12]

9.2.4. Modified SELENA Flare Index (mSFI)

The classic Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) flare index (cSFI) was originally developed for the SELENA study.[3,40] The index was designed to capture flares of all types as well as distinguishing severe flares from mild-to-moderate flares. The cSFI is a composite index that includes the following components:

- Assessment of change from baseline in global and organ-specific disease activity measures using the SELENA-SLEDAI instrument
- Increase from baseline in the Physician's Global Assessment (PGA) of disease activity
- Increase in dose or addition of new oral glucocorticoid therapy for SLE activity
- Addition of new NSAID, antimalarial, or immunomodulatory therapy for SLE activity
- Hospitalization for SLE activity

The cSFI was modified in this study (mSFI) for use with the SLEDAI-2K. Further modifications included:

- An expanded list of background therapies (MMF, belimumab, rituximab, or other immunosuppressant therapy) for SLE activity
- A modification in the definition of severe flare to ensure that at least one additional mSFI component (eg, organ-specific disease activity, added background therapy) is present if the change in SLEDAI-2K instrument score to "greater than 12" box was checked

9.2.5. Joint Count Assessments

Assessment of active joints (defined as joints demonstrating pain and signs of inflammation), tender joints, and swollen joints will be performed at visits indicated in Table 1 and Table 2. To be considered an active joint, an affected joint must be painful as reported by the subject and must demonstrate tenderness and at least one additional sign of inflammation (eg, observed swelling such as edema or effusion) on physical examination as determined by the joint assessor. Each of 64 joints will be evaluated for tenderness and 62 joints for swelling (hips are excluded for swelling).

The joint assessment should be performed by an adequately trained joint assessor. The joint assessor should preferably be a rheumatologist, but if a rheumatologist is not available, it should be a health care provider with at least 1 year of experience in performing joint assessments. A health care provider with less than 1 year of experience may serve as a joint assessor based upon the approval of the sponsor. It is strongly recommended that the same joint assessor perform these assessments at every visit. It is recommended that the designated assessor identify an appropriate back-up joint assessor in case the designated joint assessor is unavailable.

9.2.6. Cutaneous Lupus Erythematosus Disease Area and Severity Index

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 patients with or without systemic involvement.[1] The CLASI consists of 2 scores; the first summarizes the activity of the disease while the second is a measure of the damage caused by the disease (CLASI Activity and CLASI Damage scores). Activity is scored by the Investigator based on erythema, scale/hyperkeratosis, mucous membrane involvement, acute hair loss, and 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.[1]

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

9.2.7. Patient Assessment of Pain Intensity

The subject will be asked to report his or her average pain during the past Week on a 10-cm VAS with anchors 0 to represent “no pain” and 10 to represent “the worst possible pain.”

9.2.8. Lupus Quality of Life Measure

The Lupus Quality of Life (LupusQoL) is a validated SLE-specific health-related quality of life (HRQoL) instrument consisting of 34 items across 8 domains (Physical health, Emotional health, Body image, Pain, Planning, Fatigue, Intimate relationships, and Burden to others). The LupusQoL has a 5-point Likert response format, where 0 = all the time, 1 = most of the time, 2 = a good bit of the time, 3 = occasionally, and 4 = never, and uses a 4-week recall period. The mean raw domain score is transformed to scores ranging from 0 (worst HRQoL) to 100 (best HRQoL) by dividing by 4 and then multiplying by 100. A higher score reflects better HRQoL.[31]

9.2.9. FACIT-Fatigue

The Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue) version 4.0 is a 13-item questionnaire formatted for self-administration that assesses patient-reported fatigue and its impact upon daily activities and function over the past seven days. Subjects will be asked to answer each question using a 5-point Likert-type scale (0 = Not at all; 1 = A little bit; 2 = Somewhat; 3 = Quite a bit; and 4 = Very Much). The interpretation of FACIT-Fatigue scores is such that a higher score indicates *less* fatigue, with a range of possible scores of 0-52, with 0 being the worst possible score and 52 the best.[8,29] A study using a combination of approaches, including both anchor-based estimates derived from statistically significant cross-sectional and

longitudinal differences and distribution-based estimates concluded that the minimal clinically important difference in patients with SLE for the FACIT-Fatigue is between 3 and 4 points.[6] This range is similar to that which has been reported in other disease areas.[5,6,37]

9.2.10. Short-form Health Survey-36 Standard (4-Week Recall) v2

The 36-item Short-form Health Survey (SF-36) questionnaire is a self-administered generic measure of HRQoL comprising 36 items over 8 domains that cover a range of functioning:

- Limitations in physical function
- Limitations in usual role activities
- Bodily pain
- General mental health (psychological distress and well-being)
- Vitality (energy and fatigue)
- Limitations in social functioning due to physical or mental health problems
- Limitations in usual role activities due to personal or emotional problems
- General health perception

The Standard version uses a 4-week recall period and 5-point Likert response options ranging from "Excellent" to "Poor" (with the exception of the General Health item, which uses a one-year recall period, and Likert response options ranging from "Much better" to "Much worse"). The scoring yields a PCS score and an MCS score, and 8 subscale scores. The scale scores and summary scores are converted into 0-100 using a norm-based system where linear transformations are performed to transform scores to a mean of 50 and standard deviations of 10, based upon general US population norms.[57] Higher scores represent better outcomes. SF-36 can be completed in 5 to 10 minutes. The instrument has undergone extensive linguistic and cultural validation.

The concepts measured by the SF-36 are not specific to any age, disease, or treatment group, allowing comparison of relative burden of different diseases and the benefit of different treatments.[57] A change of 2.5 points in any of the subscales or 5 points for the component score is associated with clinically meaningful change.[43,58,59]

9.2.11. EuroQol EQ-5D-5L Descriptive System

The EuroQol EQ-5D-5L Descriptive System (EQ-5D-5L) is a general health-related quality of life measure comprising a descriptive system and the EQ VAS.[19]

The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, with 5-point Likert response options ranging from "I have no problems in..." to "I am unable to…". Subjects will be asked to rate their current health and functional status for each of the 5 domains. Individual patient responses to the 5 questions are collected, and responses are converted into an overall quality of life score via a preference-based statistical mapping algorithm. The scores on these five dimensions can be presented as a

health profile or can be converted to a single summary index number (utility) reflecting preferability compared to other health profiles.

Additionally, EQ-5D-5L also includes a 20-cm visual analog scale (EQ-VAS) that ranges from 100 for "best imaginable health state" to 0 for "worst imaginable health state," respectively. Respondents are asked to indicate how they rate their own health by drawing a line from an anchor box to that point on the EQ-VAS which best represents their own health on that day. This can be used as a quantitative measure of health outcome that reflects the patient's own judgement.

9.2.12. Work Productivity and Activity Impairment Scale – Lupus

The Work Productivity and Activity Impairment (WPAI) scale consists of 6 questions intended to evaluate work hours lost due to lupus disease and to assess the impact of lupus disease on work productivity and on regular daily activities. The WPAI scoring is evaluated over the prior 7 calendar days. Outcomes for each domain are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity. The WPAI-Lupus reflects the impairments due to lupus.[16]

9.2.13. Lupus Foundation of America Rapid Evaluation of Activity in Lupus (LFA-REAL)

The Lupus Foundation of America Rapid Evaluation of Activity in Lupus (LFA-REAL™) is a novel 2-part disease assessment system, based on a series of simple questions and observations, to determine a treatment's impact on the patient's health and daily life. One set of questions and observations, known as a ClinRO, is designed for clinicians; and the other set of questions, known as a PRO is designed for subjects. Both the ClinRO and PRO portions consist of anchored, landmarked VAS with a range of scores from 0-3. Domains in the ClinRO portion include mucocutaneous, musculoskeletal, cardiorespiratory, neuropsychiatric, renal, hematologic, constitutional, vasculitis, and rare other (to be filled in by the clinician). Domains in the PRO portion include symptom-based measures, including rash, arthritis, muscle symptoms, fatigue, hair loss, fever, and other body symptoms. Higher scores denote worse disease. This tool is intended to make evidence-based and targeted treatment decisions, allowing for overall as well as organ-specific disease assessment, and for comparisons between physician and patient evaluation of ongoing disease activity.[22]

9.2.14. SLICC/ACR Damage Index

The SLICC/ACR Damage Index is a validated, reliable instrument to measure organ damage after the diagnosis of lupus. The SLICC/ACR damage index evaluates 12 systems which are assessed by 41 items for damage, which is defined as non-reversible change that is not related to active inflammation and that has occurred since the onset of lupus and present for at least 6 months. Items are scored based upon evidence of damage with a maximum possible score of 47. Scores can only increase with time. If evidence of damage is noted for an item, it is given a score of 1.[14]

9.3. Efficacy Endpoint Definitions

9.3.1. SRI Composite Response

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 PGA (<10% worsening from baseline).[13] 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 the treatment failure criteria prior to Week 52. SRI-5, SRI-6, SRI-7, and SRI-8 response are defined similarly, except the SLEDAI-2K improvement from baseline is to be at least 5, 6, 7, or 8 points, respectively.

9.3.2. Lupus Low Disease Activity State

Lupus Low Disease Activity State (LLDAS) was initially developed in a single-center SLE cohort[11] to predict the non-accrual of irreversible organ damage, measured using the SLICC damage index. It was later investigated in a multi-national multi-ethnic cohort.[15] A modified definition of LLDAS is used in this study and is defined as meeting all the following conditions[33]:

- SLEDAI-2K ≤4, with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis), and no reported fever, hemolytic anemia, or gastrointestinal activity)
- No new disease activity compared with the previous assessment
- PGA ≤1 on a 0-3 scale VAS
- A current prednisone (or equivalent) dose of ≤7.5 mg daily
- Well-tolerated standard maintenance doses of permitted immunosuppressive drugs and approved biological agents

9.3.3. Definitions of Remission in Systemic Lupus Erythematosus

The on-treatment definitions of remission in systemic lupus erythematosus (DORIS) defines clinical SLE remission as determined by clinical SLEDAI-2K = 0, BILAG D or E for all systems, or clinical European consensus lupus outcome measure (ECLAM) 0, including routine laboratory assessments and PGA.[55,60] A distinction is made between remission off and on therapy. Remission can be categorized as Clinical Remission or Complete Remission (requiring negative serologies) and separately as Clinical Remission on treatment and Complete Remission on treatment. A modified definition of DORIS Clinical Remission on treatment is used in this study and is defined as meeting all the following conditions:

- SLEDAI-2K score = 0 (excluding anti-dsDNA, C3, and C4 components)
- PGA score <0.5 cm on a 10 cm, 0-3 VAS scale
- Prednisone (or equivalent) dose ≤5 mg/day
- Antimalarial, immunosuppressant, or study agent use is permitted

9.3.4. SLE Flare

For this study, SLE flares will be defined as follows:

- SLEDAI-2K flare is defined as at least 1 new SLEDAI-2K mild/moderate or severe flare compared with baseline as assessed using mSFI.
- Severe SLEDAI-2K flare is defined as presence of one or more of the following:
  - Increase in SLEDAI-2K score to greater than 12. If this is the only criteria met, at least one additional criterion below must also be present to be considered a severe SLEDAI-2K flare
  - New/Worse SLE activity (CNS, vasculitis, nephritis, myositis, thrombocytopenia ($<60,000/mm^3$), hemolytic anemia (hemoglobin <7 g/dL or decrease in hemoglobin >3 g/dL) requiring one or more of the following: (1) increase in prednisone (or equivalent) dose to >0.5 mg/kg/day, (2) a doubling or greater of prednisone (or equivalent) dose, (3) addition of a new systemic immunosuppressant agent (cyclophosphamide, AZA, MTX, MMF, belimumab, rituximab, or other systemic immunosuppressant therapy), or (4) hospitalization for SLE activity
  - Increase in prednisone (or equivalent) to >0.5 mg/kg/day for SLE activity
  - New cyclophosphamide, AZA, MTX, MMF, belimumab, rituximab (or other systemic immunosuppressant therapy) for SLE activity
  - Hospitalization for SLE activity
  - Increase in the 0-3 VAS anchored PGA score to >2.5
- Mild/moderate SLEDAI-2K flare is defined as presence of one or more of the following:
  - Increase in SLEDAI-2K score of 3 points or more (but not to more than 12)
  - New/worse SLE activity (discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus, nasopharyngeal ulcers, pleuritis, pericarditis, arthritis, fever due to SLE)
  - Increase in prednisone (or equivalent), but not to >0.5 mg/kg/day, for SLE activity
  - Added NSAID or hydroxychloroquine (or other antimalarial therapy) for SLE activity
  - Increase in the 0-3 VAS anchored PGA score by ≥1, but not to more than 2.5
- BILAG flare is defined as at least 1 new BILAG A or 2 new BILAG B domain scores not present at baseline:
- Severe BILAG flare is defined as at least 1 new BILAG A domain score not present at baseline
- Moderate BILAG flare is defined as at least 2 new BILAG B domain scores not present at baseline

The following definitions will be applied to both SLEDAI-2K and BILAG Flares:

- A flare-free visit is defined as any postbaseline visit where none of the flare criteria above are met. If a subject has any of the flare criteria listed above, he or she will not be counted as being flare free at the specific visit.

- 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.
- The annualized flare rate is the number of flares per year.

9.3.5. Reduction of Glucocorticoid Dose

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.

9.3.6. Major Clinical Response

Major clinical response is defined as BILAG C score or better in all organ domains.

9.3.7. Medical Resource Utilization

Medical resource utilization data associated with medical encounters will be collected by the Investigator and staff for subjects throughout the study. Protocol-mandated procedures, tests, and encounters are excluded. The data collected may be used to conduct economic analyses for both total and SLE-related encounters on hospitalizations, emergency room/urgent care visits, and unscheduled visits to health-care providers.

9.4. Pharmacokinetics and Immunogenicity

Serum samples will be collected for measurement of serum concentrations of ustekinumab and anti-ustekinumab antibodies at the timepoints specified in Table 1.

Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

9.4.1. Evaluations

Serum samples will be used to evaluate the PK of ustekinumab, as well as the anti-ustekinumab antibodies. Serum collected for PK and immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained.

9.4.2. Procedures and Analyses

9.4.2.1. Pharmacokinetics

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

9.4.2.2. Immunogenicity

The detection and characterization of anti-ustekinumab antibodies will be performed using a validated assay method by or under the supervision of the sponsor. All samples collected for detection of anti-ustekinumab antibodies will also be evaluated for ustekinumab serum concentration to enable interpretation of the antibody data. Anti-ustekinumab antibodies will be evaluated in serum samples collected from all subjects according to Table 1 and Table 2. Serum samples will be screened for antibodies binding to ustekinumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of ustekinumab. Serum samples that test positive for antibodies to ustekinumab will be further characterized to determine if antibodies to ustekinumab could neutralize the biological effects of ustekinumab in vitro (ie, neutralizing antibodies [NAbs] to ustekinumab). All samples will be tested by the sponsor or sponsor's designee.

9.5. Biomarkers

Assessments will be performed to identify biomarkers that are relevant to ustekinumab treatment and/or SLE. These may include, but are not limited to, inflammatory protein markers, RNA, cellular markers and, for patients who complete the optional DNA informed consent, DNA markers.

The collection, preparation, storage, and shipment of blood and serum for biomarker analysis are detailed in the Laboratory Manual.

9.5.1. Serum Analyses

Serum will be analyzed for levels of specific proteins, auto-antibodies, and other inflammation-related molecules and/or disease-associated serologies (see Section 11.7).

9.5.2. Whole Blood Gene Expression

Whole blood will be collected from all subjects for RNA expression analysis. Total RNA will be isolated and used for differential gene expression analyses to identify gene expression patterns that are relevant to ustekinumab treatment and/or SLE, and to evaluate markers that can predict clinical response.

9.5.3. Peripheral Blood Mononuclear Cells (Cellular Analysis)

Whole blood will be collected and processed to peripheral blood mononuclear cells (PBMC) and cryopreserved for analysis. Analysis may include but is not limited to flow cytometric

assessment of cell populations or functional assessment of cells in response to ustekinumab treatment and/or SLE pathogenesis.

9.6. Pharmacogenomic (DNA) Evaluations

Genetic (encoded DNA sequence) variation may be important contributory factors to interindividual differences in drug disposition, response, and clinical outcomes. Genetic (DNA) factors may also serve as markers for disease susceptibility and prognosis and may identify population subgroups that respond differently to a drug. DNA samples will be analyzed for identification of genetic factors to better understand the molecular effects of ustekinumab and/or SLE, and to evaluate markers that can predict clinical response. Genetic (DNA) research may consist of the analysis of 1 or more candidate genes or analysis of the entire genome (as appropriate) in relation to ustekinumab and/or SLE.

Only subjects who sign the optional consent form to participate in the genetic assessment will have whole blood DNA samples collected and analyzed.

9.7. Safety Evaluations

Safety evaluations will include assessment of AEs, concomitant medications, pregnancy testing (see Section 12.3.3), administration reactions, chemistry and hematology laboratory tests, immunogenicity, vital signs, and general physical examinations. In addition, electrocardiogram (ECG), chest x-ray (consistent with local regulations), HIV, hepatitis B, hepatitis C, and TB testing will be required at screening (Table 1 and Table 2). Refer to Section 4.1 for TB screening criteria. Any clinically relevant changes that occur during the study must be recorded on the AE section of the eCRF. Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the Investigator until resolution or until a clinically stable endpoint is reached. Details regarding the DMC are provided in Section 11.10.

The study will include the following evaluations of safety and tolerability according to specific time points provided in Table 1 and Table 2.

9.7.1. Adverse Events

See Section 12.1 for AE definitions. Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the Investigator as specified in Section 12, Adverse Event Reporting.

9.7.1.1. Infections

Subjects will be counseled on the signs and symptoms of infections and will be instructed to contact the site between scheduled visits should any signs and symptoms occur. At each site visit, Investigators or other site personnel are required to evaluate subjects for any signs or symptoms of infection and ask about symptoms of infection or other AEs that may have occurred between site visits.

Study agent should not be administered to a subject with a clinically important, active infection. Treatment with study agent should be withheld until serious and/or severe infections are completely resolved. If a subject develops a serious or severe infection, including but not limited to sepsis or pneumonia, discontinuation of study agent must be considered. Treatment must be permanently discontinued for subjects who develop a serious opportunistic infection. This should be discussed with the medical monitor and/or sponsor. For active varicella zoster infection or a significant exposure to varicella zoster infection in a subject without history of chickenpox, the subject should be evaluated for symptoms of infection and if the subject has received appropriate treatment and/or recovered or has no symptoms of infection, he/she may continue study agent after discussion with the medical monitor and/or sponsor.

9.7.1.1.1. Tuberculosis

Any newly identified case of active TB occurring after the first administration of study agent(s) in subjects participating in this clinical study must be reported by the Investigator according to the procedures in Section 9.1.3.2. Investigators are also advised that active TB is considered a reportable disease in most countries. These events are to be considered serious only if they meet the definition of a serious adverse event. Treatment must be permanently discontinued for subjects with active TB.

9.7.1.2. Infusion or Injection-site Reactions

An infusion reaction is defined as an AE that occurs during or within 1 hour following the infusion of study agent, excluding laboratory abnormalities. Subjects should be monitored for the occurrence of infusion reactions for at least 1 hour after IV infusion and injection-site reactions for at least 30 minutes following SC injection (if subject received SC injection at the study site; see Table 1 and Table 2). Permanent discontinuation of study agent must be considered for subjects who experience an adverse event of infusion reaction that is considered serious or severe by the Investigator.

Subjects should be instructed in the signs, symptoms, and care of injection-site reactions before they begin at-home administration of study agent during the extension period.

9.7.2. Clinical Laboratory Tests

Blood samples for serum chemistry, coagulation, and hematology will be collected as shown in Table 1 and Table 2.

The Investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event Section of the eCRF. The laboratory reports must be filed with the source documents. With prior sponsor approval, local laboratories may be used in the event of a safety concern or if initiation of treatment is critical and the central laboratory results are not expected to be available before the need to provide study agent or take action to ensure subject safety.

The following tests will be performed by the central laboratory (unless otherwise specified):

- **Hematology Panel**

  -Hemoglobin
  -Hematocrit
  -White blood cell (WBC) count with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils)
  -Platelet count
  -CD 19 B-cell analyses by flow cytometry during screening only if needed for subjects previously exposed to B–cell depleting therapies)
  -Coomb's direct test (performed locally)

- **Serology Laboratory**

  -Ig isotype profile (IgG, IgM, IgA levels)
  -C3 and C4 Complement
  -ANA
  -Anti-dsDNA
  -Anti-phospholipid antibodies including lupus anticoagulant, anti-cardiolipin, and anti-β_2-glycoprotein-I antibodies
  -Other autoantibodies including anti-Smith, anti-Sjögren's-syndrome-related antigen A (SSA anti-Ro, and B (SSB anti-La), anti-ribonucleoprotein (anti-RNP), rheumatoid factor, and anti-cyclic citrullinated peptide (CCP)

- **Coagulation Labs**

  -Prothrombin Time
  -Partial Thromboplastin Time
  -International Normalized Ratio

- **Serum Chemistry Panel**

  -Sodium
  -Potassium
  -Chloride
  -Bicarbonate
  -Blood urea nitrogen
  -Creatinine
  -Nonfasting glucose
  -Aldolase (if creatine kinase is elevated at screening then perform aldolase test at screening, Week 0, and follow-up as needed)
  -FSH as needed
  -Alkaline phosphatase
  -Calcium
  -Phosphorous
  -Albumin
  -Total protein
  -Creatinine kinase
  -Aspartate aminotransferase
  -Alanine aminotransferase
  -total bilirubin, and if total bilirubin is abnormally elevated, then direct bilirubin, and indirect bilirubin

- **Urine Analyses** – Fresh spot urine
  - Urinalysis using urine dipstick. Urine sample will be further analyzed.
  - Urinary protein/creatinine ratio[10] will be analyzed using an aliquot of spot urine collected from subjects.
  - Urine sediment microscopy (assessment using spot urine samples), with features analyzed to include:

    -Red blood cells
    -WBC
    -Epithelial cells
    -Crystals
    -Red blood cells, WBC, or heme-granular casts
    -Bacteria

- Urine pregnancy testing for women of childbearing potential only (performed locally)
- Serum pregnancy test (at the discretion of the Investigator)
- Viral serology (HIV antibody, HBsAg, anti-HBs, anti-HBc total, and HCV antibody)
- QuantiFERON® -TB test
- TB skin test (where applicable; performed locally)

Dipstick and sediment analysis of the urine samples will be performed in parallel, ie, in the same sample at the same time. Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, and urobilinogen will be determined using a dipstick. Red blood cells, WBC, epithelial cells, crystals, casts, and bacteria will be measured using flow cytometry or microscopy. If there is discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically. Crystals, and bacteria will only be reported if they are present. Casts will be reported whether or not they are present.

9.7.3. Electrocardiogram

A 12-lead ECG will be performed locally at screening. During an ECG, it is recommended that subjects be in a quiet setting without distractions (eg, television, cell phones), resting in a supine position for at least 5 minutes before ECG recording, and refraining from talking or moving arms or legs. If blood sample collection or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG, vital signs, blood sample collection. If an abnormal result is obtained, the ECG may be repeated.

9.7.4. Vital Signs

Weight, temperature, pulse/heart rate, respiratory rate, blood pressure will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

9.7.5. Physical Examination

A full-body physical examination will be performed pretreatment and during the study as shown in Table 1 and Table 2. A full-body physical examination includes assessment of general appearance, head (including oral cavity and dentition), eyes, ears, nose, throat, neck, abdomen, lymph nodes, and peripheral extremities and the following systems: cardiovascular (including peripheral vascular), respiratory, neurologic, musculoskeletal, skin, genitourinary (if clinical history indicates need).

A targeted physical examination will be performed pretreatment and during the study as shown in Table 1 and Table 2. A targeted physical examination includes assessment of general appearance, head (including oral cavity and dentition), eyes, nose, throat, abdomen, lymph nodes, and the following systems: cardiovascular (including peripheral vascular), respiratory, neurologic, musculoskeletal, and skin.

9.7.6. Pregnancy

Female subjects of childbearing potential are to be monitored for possible pregnancy using a urine dipstick test performed at the clinical site as shown in Table 1 and Table 2. Additional serum hCG testing may also be performed locally or at the central lab if desired by the study Investigator. See Section 12.3.3 for details on reporting pregnancies that occur during the study. Pregnancies (of the study subject or if the subject is male, then the subject's partner) must be followed to determine the outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the subject was discontinued from the study early.

9.8. Cutaneous Disease Photography Substudy

In order to correlate CLASI assessment findings with images of cutaneous lupus, a cutaneous disease photography substudy will be performed at selected sites on a subset of subjects with cutaneous lupus present at baseline. There will be no restrictions on the number of subjects with cutaneous disease who can enroll in the substudy. Subjects with cutaneous disease will be asked to provide consent for medical photographs to be collected from identified cutaneous lesions or areas of active disease (see Table 1).

Photography equipment and services will be provided by the photography vendor to document cutaneous disease. For standardization across investigative sites and visits, all study photographs will be captured using the equipment, supplies, and guidelines provided by the photography vendor. Images will be uploaded to a secure website hosted by the photography vendor and monitored for technical quality. Detailed instructions for all aspects of the photography procedures will be supplied separately in the Investigator user manuals to be provided by the photography vendor. Confidentiality of the subjects involved in this study will be maintained; specifically, photographs of subjects in this study will not be published or otherwise made public without blocking adequate portions of the subject’s face or body so that the individual cannot be identified.

9.9. Sample Collection and Handling

The actual dates and times of sample collection should be recorded in the eCRF or laboratory requisition form. Refer to Table 1 and Table 2 for the timing and frequency of all sample collections.

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

10. SUBJECT COMPLETION / DISCONTINUATION OF STUDY AGENT / WITHDRAWAL FROM THE STUDY

10.1. Study Completion

A subject will be considered to have completed the double-blind phase of the study if he or she has completed assessments through Week 52.

A subject will be considered to have completed the extension period of the study if he or she has completed assessments through Week 160.

10.2. Discontinuation of Study Agent/Withdrawal from the Study

10.2.1. Discontinuation of Study Agent

A subject will not be automatically withdrawn from the study if he or she has to discontinue study agent before the end of the treatment regimen.

A subject's study agent must be discontinued if:

- The Investigator, sponsor, and/or medical monitor believes that for safety reasons or tolerability reasons (eg, adverse event), or due to severe, unstable, or rapidly progressive SLE disease activity, it is in the best interest of the subject to discontinue study agent.
- The subject becomes pregnant
- The subject experiences an AE temporally associated with study agent infusion or injection, resulting in bronchospasm with wheezing and/or dyspnea requiring ventilatory support, or symptomatic hypotension with a greater than 40 mm Hg decrease in systolic blood pressure.
- The subject develops study agent hypersensitivity (eg, anaphylaxis, angioedema) reaction that is reported as serious or severe.
- The subject is diagnosed with a malignancy, with the exception of no more than 2 localized basal cell skin cancers that are treated with no evidence of recurrence or residual disease.
- The subject is deemed ineligible according to the following TB criteria:
  - A diagnosis of active TB is made.

- A subject has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination, or has had recent close contact with a person with active TB, and cannot or will not continue to undergo additional evaluation.
- A subject undergoing evaluation has a chest radiograph with evidence of current active TB and/or a positive QuantiFERON®-TB test result (and/or a positive tuberculin skin test result in countries in which the QuantiFERON®-TB test is not approved/registered or the tuberculin skin test is mandated by local health authorities), unless active TB can be ruled out and appropriate treatment for latent TB can be initiated prior to the next administration of study agent and continued to completion. Indeterminate QuantiFERON®-TB test results should be handled as in Section 4.1.1. Subjects with persistently indeterminate QuantiFERON®-TB test results may continue without treatment for latent TB if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the subject has no additional risk factors for TB as determined by the Investigator. This determination must be promptly reported to the sponsor's medical monitor and recorded in the subject's source documents and initialed by the Investigator.
- A subject receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.

- The subject develops a serious opportunistic infection.
- If a new immunomodulator that is permitted per-protocol is initiated, then a subject will be considered a treatment failure but will not need to be discontinued from the study. However, if a subject requires a prohibited therapy such as a non-permitted immunomodulator, biologic, cyclophosphamide, IV glucocorticoid, or high dose glucocorticoid (see Section 8.1.7) then the subject must be discontinued from the study. Addition of new therapy for SLE activity must be discussed with the medical monitor and/or sponsor to determine the suitability of the subject to continue participating in the study.

If a subject discontinues study agent for any reason before the end of the double-blind phase, end-of-treatment assessments should be obtained and scheduled assessments should be continued.

10.2.2. Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent
- Death
- Other

If a subject is lost to follow-up, every reasonable effort should be made by the study-site personnel to contact the subject and determine the reason for discontinuation/withdrawal. Due diligence should include repeated telephone calls, certified letters, and email requests. Measures taken to obtain follow-up information must be documented.

When a subject withdraws from the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study agent assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw from this study will not be replaced.

If the reason for withdrawal from the study is withdrawal of consent then no additional assessments are allowed.

10.3. Withdrawal from the Use of Research Samples

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

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

Withdrawal from the Optional Research Samples while Remaining in the Main Study

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

Withdrawal from the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF and in the separate ICF for optional research samples.

11. STATISTICAL METHODS

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

Descriptive statistics (eg, mean, median, standard deviation, interquartile range, minimum, maximum) will be used to summarize continuous variables. Numbers and percentages will be used to summarize categorical variables. Median values will be reported for time to event variables. In addition, graphical data displays (eg, line plots) and subject listings may also be used to summarize/present the data.

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

In general, all statistical tests will be performed at a 2-sided significance level of α=0.05.

11.1. Subject Information

11.1.1. Demographics and Baseline Characteristics

For all subjects who receive at least 1 dose of study agent, descriptive statistics will be provided.

Demographics and baseline disease characteristics will be summarized based on the randomized analysis set. Descriptive statistics (mean, standard deviation, median, and range) will be provided for the subjects' age, SLEDAI-2K score, PGA score, weight, and height. Subject sex, race, concomitant medication use, number of BILAG A or BILAG B criteria, positivity for ANA, anti-dsDNA, or anti-Smith autoantibodies, number with low complement C3 or C4 levels will be summarized as frequency distributions by treatment group. Prior and concomitant medications used at baseline will be listed.

11.1.2. Disposition Information

Disposition information will be summarized by treatment group by numbers of subjects randomized, treated, and completing scheduled visits. Disposition information will be based on the randomized analysis set. Additionally, the number of subjects who discontinued study agent and the reason for discontinuation as well as those who terminated the study and reason for termination will be summarized.

11.1.3. Treatment Compliance

Study agent will be administered as an IV (initial dose) and SC injection by an authorized and qualified staff member and the details of each administration will be recorded in the eCRF including date, start and stop times for infusion and start time for injection. Compliance with the treatment assignments will be controlled by the study site personnel. Subjects will be required to record in their subject diaries, all doses of study agent that are administered at home.

11.1.4. 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.

11.1.5. Protocol Deviations

Major protocol deviations will be tabulated by treatment group in the following categories:

Subjects who "entered but did not satisfy entry criteria" or "received wrong treatment or incorrect dose" or "developed withdrawal criteria but not withdrawn" or "received a disallowed concomitant medication" and "other study procedures."

11.1.6. Prior and Concomitant Medications

Background medication use for active SLE will be summarized by treatment group. Subjects initiating new medications or changes in dose (increasing or decreasing) of medication for active SLE during the study will be summarized over time. Subjects with increases in medication will be listed. Subject diary cards will be used to capture changes in subject-administered medications that occur in between study visits, and these changes should also be recorded in the concomitant therapy section of the eCRF.

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).

11.2. Sample Size Determination

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[53,54] and is consistent with the results observed in CNTO1275SLE2001.

The power to detect a significant treatment difference at α=0.05 (2-sided) is calculated under various assumptions (Table 7).

Table 7: 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.[12,34]

This sample size of 500 is based on (1) the sample size needed to power the study appropriately, (2) increasing the ability to have adequate numbers of subjects for subgroup analyses and, (3) maintaining appropriate safety exposure in accordance with International Conference on Harmonisation (ICH) guidelines. Differences in racial/ethnic background have been noted in biomarkers, such as the Type I IFN signature response and in response rates to SLE treatment. Sizing will accommodate investigation of biomarkers in these subgroups, to better characterize impact on disease signaling in diverse patient populations, and its relationship to clinical response to study agent.

If the primary endpoint analysis is significant, subsequent analyses will hold to the standard α level control of a pivotal study (ie, 2-sided α level of 0.05 for major secondary endpoints). The major secondary endpoints will be tested sequentially according to the order specified in the protocol. If the previous endpoint is not statistically significant, subsequent endpoint(s) will not be tested and nominal p-values will be provided.

11.3. Analysis Sets

The primary efficacy analysis set will be based upon the Full Analysis Set (FAS), defined as randomized subjects who receive at least 1 dose (partial or complete, IV or SC) of ustekinumab or placebo and will be analyzed based on randomized treatment groups, regardless of the treatment received.

The safety analysis set will include all randomized subjects who receive at least 1 dose (partial or complete, IV or SC) of ustekinumab or placebo and subjects will be analyzed based on the treatment they received, regardless of the treatment groups to which they were assigned.

The PK analysis set will include all subjects who receive at least 1 complete dose of ustekinumab and have at least one post initial dose sample collection.

The immunogenicity analysis set is defined as all subjects who received at least 1 dose (partial or complete) of ustekinumab and have at least one post initial dose sample collection. Subjects will be analyzed according to the actual treatment received.

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.

11.4. Efficacy Analyses

In general, for treatment response efficacy endpoints, treatment comparisons will be performed using a logistic regression model, adjusting for baseline stratification factors, baseline SLEDAI-2K score, and region. In general, for continuous efficacy endpoints, treatment comparisons will be performed using either an MMRM model or an analysis of covariance model. All the models will include treatment group, adjustments for baseline stratification factors, baseline SLEDAI-2K score, and region as appropriate, and may include baseline values of the dependent variable as explanatory factors.

11.4.1. Primary Endpoint Analysis

Analyses of the primary efficacy endpoint (SRI-4 composite response at Week 52) will include data from all randomized subjects who received at least 1 dose of study agent based on their assigned treatment group regardless of the actual treatment received. The primary analysis will be based upon the composite estimand where subjects meeting treatment failure criteria are assumed nonresponders from the point of treatment failure forward, and missing data are assumed as nonresponse.

The SRI-4 composite 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 PGA.[12,34] Subjects who meet 1 or more treatment failure criteria prior to Week 52 will be considered SRI-4 nonresponders at Week 52 regardless of the observed SRI-4 response status.

Logistic regression, adjusting for baseline stratification factors, region, and baseline SLEDAI-2K, will be used to analyze the primary endpoint. The logistic regression model will include treatment group and stratification factors. The baseline SLEDAI-2K value will be defined as the closest nonmissing measurement taken prior to the Week 0 infusion. See the SAP for further details about the analysis of the primary endpoint, including sensitivity analyses.

11.4.1.1. Subgroup Analyses

Subgroup analysis of the primary endpoint based on region may be performed. This is due to potential regional differences in evaluating efficacy, and high placebo response rates in certain regions. Subgroup analysis of the primary endpoint by other selected baseline characteristics may be presented:

- Age
- Race
- Baseline SLE Medications and SLEDAI-2K (combined) Score
- Baseline lupus nephritis
- Weight
- Body mass index

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

11.4.2. Major Secondary Analyses

With the order specified in Section 2.2.2, each of the secondary endpoints will be tested at a 2-sided α level of 0.05 if significance is achieved for the preceding hypothesis. 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.

11.4.3. Other Planned Efficacy Analyses

Other endpoints (see Section 2.2.3) will be summarized over time by treatment group. Treatment comparisons will be performed at Week 24 and Week 52. The methods of analysis and the data-handling rules will be provided in the SAP.

11.4.4. Handling Missing Data

For the primary endpoint, subjects with missing data or meeting treatment failure criteria will be imputed as nonresponders. Sensitivity analyses will be performed and include (1) considering primary endpoint data for subjects meeting treatment failure criteria as missing and (2) using observed data regardless of whether the subject met treatment failure criteria. In both sensitivity analyses, missing response will be imputed by multiple imputation methods (eg, serial logistic regression) under the assumption of missing at random.

For binary major secondary endpoints, analyses will be similar to the analysis of the primary endpoint: subjects with missing data or meeting treatment failure criteria will be imputed as nonresponders. For other secondary endpoints, observations after meeting treatment failure criteria will be set to missing for subjects who met the criteria. No imputation will be performed for missing postbaseline continuous values; the statistical model (ie, MMRM) will adjust for missing data.

For all other endpoints, observations after meeting treatment failure criteria will be set to missing for subjects who met the criteria. For binary endpoints, missing data will be imputed using multiple imputation methods (eg, serial logistic regression) under the assumption of missing at random. For continuous endpoints, the statistical model (ie, MMRM) will adjust for missing data.

11.4.5. Treatment Failure Criteria

Subjects who meet 1 or more of the following criteria (due to increased SLE disease activity) will be defined as treatment failures from the time the treatment failure occurs onward:

- Exceed the baseline dose of permitted SLE medications (eg, antimalarials, immunosuppressants, glucocorticoids) between the Week 12 and the Week 52 visits
- Initiate a new permitted SLE medication (eg, antimalarials, immunosuppressants, glucocorticoids) between the Week 12 and Week 52 visits. A "new" SLE medication is one that was not present at randomization or is not a replacement for (in the same class as) a medication present at randomization at an equivalent or lower dose (see note below)
- Initiate a new protocol-prohibited medication (eg, intravenous glucocorticoid exceeding 625 mg prednisone equivalent/day for 2 or more days, disallowed route of systemic glucocorticoid administration, systemic immunomodulators, cytotoxic agent, biologic agent) at any time between randomization and the Week 52 visit
- Discontinue study agent for any reason prior to Week 52

Note: Substitution of an agent with a similar mechanism of action at an equivalent or lower dose will not be considered a treatment failure (eg, MMF substitution for MPA or vice versa, AZA substitution for 6-MP or vice versa, glucocorticoid substitutions for other glucocorticoids). In addition, MTX oral can replace MTX subcutaneous (or intramuscular) or MTX subcutaneous (or intramuscular) can replace MTX oral).

Further details of data handling rules, including treatment failure criteria, will be presented in the SAP.

11.5. Pharmacokinetic Analyses

Serum ustekinumab concentrations will be summarized over time. Descriptive statistics, including arithmetic mean, standard deviation, median, interquartile range, minimum, and maximum will be calculated at each sampling time point. All concentrations below the lowest quantifiable sample concentration of the assay (BQL) or missing data will be labeled as such in the concentration data listing or statistical analysis system (SAS) dataset. The BQL concentrations will be treated as zero in the summary statistics.

If feasible, population PK analysis of ustekinumab may be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline subject characteristics (demographics, laboratory variables, disease characteristics, etc) will be tested as potential covariates affecting PK

parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

11.6. Immunogenicity Analyses

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

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

The incidence of NAbs to ustekinumab will be summarized for subjects who are positive for antibodies to ustekinumab and have samples evaluable for NAbs to ustekinumab.

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

11.7. Pharmacodynamic and Biomarker Analyses

Biomarker analyses may be performed, including serum analysis for levels of IFN as well as molecular pathway profiling for evidence of IL-12 and IL-23 pathway modulation. The biomarkers analyzed may include inflammatory markers, RNA, auto-antibodies, T, B, and NK cell immunophenotyping, and other categories of biomarkers potentially involved in the development and the progression of SLE.

Analytes may include (but are not limited to):

- Type I, II, and III IFNs
- IL-6
- C-X-C motif chemokine 10 (CXCL10)
- Antibodies associated with coagulopathy
- Immunoglobulin characterization
- BAFF, also known as BLyS
- Other inflammation-related molecules
- Other known SLE auto-antibodies (ANA, anti-Smith antibody, anti-SSA [anti-Ro], and anti-SSB [anti-La])
- Subject whole blood IFN signature response

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

Genetic (DNA) analyses will be conducted only in subjects who sign the optional DNA consent form. These analyses will be summarized in a separate technical report.

11.8. Pharmacokinetic and Pharmacodynamic Analyses

11.8.1. Pharmacokinetic/Pharmacodynamic Evaluations

If data permit, the relationship between serum ustekinumab concentration and efficacy or PD measures may be analyzed graphically. In addition, population PK/PD modeling may be performed to characterize the relationship between serum ustekinumab exposure and efficacy measures. Further details will be provided in a population PK/PD analysis plan and the results will be summarized in a separate report.

11.9. Safety Analyses

Safety analyses will include summaries of discontinuations, deaths, AEs, SAEs, and clinical laboratory tests. Targeted safety events in SLE, based on mechanistic plausibility (eg, serious infections, opportunistic infections, TB, hypersensitivity reactions) or potential population risks (eg, worsening of renal or CNS disease) will also be summarized.

11.9.1. Adverse Events

The verbatim terms used in the eCRF by Investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are adverse events with onset during the treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported adverse events will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate. The incidence, severity, and types of infections, infusion reactions, and injection-site reactions will be analyzed for this study.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event.

11.9.2. Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the changes from baseline Changes from baseline results will be presented in pre- versus posttreatment cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the abnormalities will be made. A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided.

11.10. Interim Analysis

A futility analysis will be carried out 24 weeks after approximately 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 (eg, other endpoints, other time points) may also be considered. The details of the futility analysis will be included in the SAP. As this is a futility analysis and the study will not be stopped early to claim success, no alpha adjustment will be implemented due to the futility analysis.

11.11. Data Monitoring Committee

An independent DMC will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study. The committee will meet periodically to review interim data. After the review, the DMC will make recommendations regarding the continuation of the study. The details will be provided in a separate DMC charter.

In addition to regular safety reviews, the DMC will perform a futility analysis 24 weeks after approximately 50% of the planned subjects have been randomized. After reviewing the data, the DMC will make a recommendation to the Sponsor Committee, which is independent of the study team, based on the predefined futility rules (details are included in the SAP and the DMC Charter). The possible recommendations are (1) to stop the study for futility or (2) continue the study without modification. The Sponsor Committee will then communicate the final decision to the study team.

The DMC will consist of at least one medical expert in the relevant therapeutic area and at least one statistician. The DMC responsibilities, authorities, and procedures will be documented in its charter.

12. ADVERSE EVENT REPORTING

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

Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events or serious adverse events. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

Solicited Adverse Events

Solicited adverse events are predefined local and systemic events for which the subject is questioned specifically (see Section 9.1.1, Overview).

Unsolicited Adverse Events

Unsolicited adverse events are all adverse events for which the subject is not questioned specifically.

12.1. Definitions

For a definition of medical device incidents and procedures for documenting them, see Attachment 5.

12.1.1. Adverse Event Definitions and Classifications

Adverse Events

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per ICH)

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Results in serious injury/death possibly caused by device malfunction
- Results in medical or surgical intervention to prevent permanent impairment or damage caused by device malfunction.
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study agent and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For ustekinumab, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure. For standard-of-care background therapies with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the package insert/summary of product characteristics.

Adverse Event Associated with the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Not Related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The Investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a sponsor study agent that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study agent
- Suspected abuse/misuse of a sponsor study agent
- Accidental or occupational exposure to a sponsor study agent
- Unexpected therapeutic or clinical benefit from use of a sponsor medicinal product
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study agent, eg, name confusion)
- Exposure to a sponsor study agent from breastfeeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the eCRF.

12.3. Procedures

12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure, which may include contact for follow-up of safety. Serious adverse events, including those spontaneously reported to the Investigator within 16 weeks after the last

dose of study agent, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an Investigator beyond the time frame specified in the protocol.

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Attachment 3 (and consistent with local guidelines).

All adverse events, regardless of seriousness, severity, or presumed relationship to study agent, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the Investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). For anticipated events reported as individual serious adverse events the sponsor will make a determination of relatedness in addition to and independent of the Investigator’s assessment. The sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the sponsor has determined there is a reasonable possibility that the drug caused a serious anticipated event, they will submit a safety report in narrative format to the Investigators (and the head of the investigational institute where required). The Investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating Investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the eCRF, which must be completed and reviewed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be transmitted electronically or by facsimile (fax).

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study agent or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- For convenience, the Investigator may choose to hospitalize the subject for the duration of the treatment period.

The cause of death of a subject in a study within 16 weeks of the last dose of study agent, whether or not the event is expected or associated with the study agent, is considered a serious adverse event.

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition (refer to Section 12.1.1, Adverse Event Definitions and Classifications).

12.3.3. Pregnancy

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

Because the effect of the study agent on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.3.4. Events of Special Interest

Adverse events of special interest: infusion or hypersensitivity reactions, serious infections, opportunistic infection (ie, infection by an organism that normally is not pathogenic or does not cause invasive infection in immunocompetent hosts), or case of active TB occurring after the first administration of study agent in subjects participating in this clinical study must be reported by the Investigator following procedures. Investigators are also advised that active TB is considered a reportable disease in most countries. These events are to be considered serious only if they meet the definition of an SAE as shown in Section 12.1.1.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, Investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY AGENT INFORMATION

14.1. Physical Description of Study Agent(s)

14.1.1. Intravenous Administration

The ustekinumab supplied for this study is a single-use, sterile solution in 30 mL vials with 1 dose strength (ie, 130 mg in 26 mL nominal volume). In addition to ustekinumab, the solution contains 10 mM L-histidine, L-histidine monohydrochloride monohydrate, 8.5% (w/v) sucrose, 0.04% (w/v) polysorbate 80, 0.4 mg/mL L-methionine, and 20 µg/mL ethylenediaminetetraacetic acid (EDTA) disodium salt dihydrate at pH 6.0. No preservatives are present. It will be manufactured and provided under the responsibility of the sponsor.

Placebo administrations will have the same appearance as the respective ustekinumab administrations. Matching placebo for final vialed product (IV) is supplied as single-use, sterile solution in 30 mL vials with a 26 mL nominal volume. The composition of the placebo is 10 mM L-histidine, L-histidine monohydrochloride monohydrate, 8.5% (w/v) sucrose, 0.04% (w/v) polysorbate 80, 0.4 mg/mL L-methionine, and 20 µg/mL EDTA disodium salt dihydrate at pH 6.0. No preservatives are present.

Body weight-range based dosing will allow administration of complete vials to subjects to simplify dose calculation and reduce the potential for errors in dosing. This body weight-range based IV dosing is intended to achieve drug exposure similar to that observed with weight-range based dosing at ~6 mg/kg. Comparable numbers of vials will be administered to subjects receiving placebo based on their body weight. The body weight-range based doses are based on the following:

- Body weight ≤55 kg: 260 mg ustekinumab (2 vials)
- Body weight >55 kg and ≤85 kg: 390 mg ustekinumab (3 vials)
- Body weight >85 kg: 520 mg ustekinumab (4 vials)

14.1.2. Subcutaneous Administration

Ustekinumab will also be supplied as a single-use prefilled syringe (PFS) in a strength of 90 mg in 1 mL nominal volume for SC administration. Each 1 mL of ustekinumab solution in the PFS contains 90 mg ustekinumab with nominal excipient concentrations of 6.7 mM L-histidine, 7.6% (w/v) sucrose, 0.004% (w/v) polysorbate 80, at pH 6.0. No preservatives are present. The needle cover on the PFS contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

Placebo administrations will have the same appearance as the respective ustekinumab administrations. Liquid placebo will also be supplied in a 1 mL PFS, and have a composition 10 mM L-histidine, 8.5% (w/v) sucrose, 0.004% (w/v) polysorbate 80, at pH 6.0. No preservatives are present. The needle cover on the PFS contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

14.2. Packaging

The investigational supplies will be uniquely packaged to assure that they are appropriately managed throughout the supply chain process. The study agent will be packaged in individual subject kits. Each kit will consist of a single vial or PFS packaged inside a protective outer carton.

Study agent will not be dispensed in child-resistant packaging.

14.3. Labeling

Study agent labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

All study agent must be stored at controlled temperatures ranging from 2°C to 8°C (36°F to 46°F), not frozen, and protected from light. Allowable temperature excursions are described in the Temperature out of Range (TOR) document. Vigorous shaking of the product should be avoided. Prior to administration, the product should be inspected visually for particulate matter and discoloration. If discoloration (other than a slight yellow color), visible opaque particles, or other foreign particles are observed in the solution, the product should not be used.

Study agent in glass vials or PFS will be ready to use. The infusions will be prepared according to the subject's treatment assignment and weight (for weight-range based infusions). The pharmacist (or designated personnel) will prepare the required volume of study agent to be infused using the appropriate number of vials.

Aseptic procedures must be used during the preparation and administration of the study material. Exposure to direct sunlight should be avoided during preparation and administration.

Refer to the pharmacy manual/study site IP and procedures manual for additional guidance on study agent preparation, handling, and storage.

14.5. Drug Accountability

The Investigator is responsible for ensuring that all study agent received at the site is inventoried and accounted for throughout the study. The study agent administered to the subject must be documented on the drug accountability form or in the drug accountability system as applicable. All study agent will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study agent containers.

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

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

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

15. STUDY-SPECIFIC MATERIALS

The Investigator will be provided with the following supplies:

- Investigator's Brochure
- Study site IP and procedures manual
- Laboratory manual(s) and laboratory supplies
- Medical Photography manual
- Certain Clinical Outcome Assessments (COAs; includes both PROs and ClinROs) will be collected using an electronic device while others will be collected on paper worksheets. Therefore, the following materials will be provided:
  - COA questionnaires and completion instructions. The following ClinROs and PROs will be collected on the paper worksheets provided:
    - ClinROs:
      - SLEDAI-2K RI-50
      - BILAG

- mSFI
- CLASI
- LFA REAL – ClinRO portion
- SLICC/ACR Damage Index

o PROs:

- LFA REAL – PRO portion. Collection only in US for native English speakers.

– Electronic COA device and user manual. The following ClinROs and PROs will be collected using an electronic device:

o ClinROs:

- PGA VAS
- Joint count assessment (used to obtain number of active joints for entry into SLEDAI-2K-RI50)

o PROs:

- Patient Assessment of Pain Intensity VAS
- FACIT-Fatigue
- SF-36 v2
- EQ-5D-5L Descriptive System
- LupusQoL
- WPAI-Lupus

- IWRS user guide and worksheets
- eCRF completion guidelines
- Sample ICFs
- Subject diary card
- Any other manual or guideline that is deemed necessary for good execution of the study

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

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

When referring to the signing of the ICF, the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the child with authority to authorize participation in research. For each subject, his or her parent(s) (preferably both parents, if available) or legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically subjects 7 years of age and older, depending on the institutional policies. For the purposes of this study, all references to subjects who have provided consent (and assent as applicable) refers to the subjects and his or her parent(s) or the subject's legal guardian(s) or legally acceptable representative(s) who have provided consent according to this process. Minors who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parents still want them to participate.

The total blood volume to be collected is considered an acceptable amount of blood to be collected over this period from the population. The total blood volume to be collected from each subject over the course of the double-blind period of the study through Week 64 follow-up will be approximately 730 mL over 1 year, which is less than 2 typical blood donations of 500 mL each. The total blood volume to be collected in the study extension between Weeks 56 and 176 will be approximately 140 mL.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

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

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

16.2.2. Independent Ethics Committee or Institutional Review Board

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

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials

- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

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

Approval for the collection of optional pharmacogenetics and/or cutaneous skin biopsies for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study agent
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the Investigator's care
- Notification if a new Investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

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

At the end of the study, the Investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent and Assent Form

Each subject (or a legally acceptable representative) must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) and assent form that are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

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

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

Assent must be obtained from children (minors) capable of understanding the nature of the study, depending on the institutional policies. A separate assent form written in language the subject can understand should be developed for subjects who are not considered to be adults legally (per local requirements). After having obtained the assent, a copy of the assent form must be given to the subject, and to the subject's parent or, if applicable, legally acceptable representative.

Subjects must be able to read and write and give informed consent/assent without assistance. A subject who is unable to read or write or to give informed consent/assent is not eligible to participate in the study.

16.2.4. Privacy of Personal Data

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

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alternative must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

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

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

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

16.2.5. Long-term Retention of Samples for Additional Future Research

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

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3, Withdrawal From the Use of Samples in Future Research.

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

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

During the study, in situations where a departure from the protocol is unavoidable, the Investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Prestudy Documentation

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

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

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

- Completed Investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

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

The subject identification and enrollment log will be treated as confidential and will be filed by the Investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth (as allowed by local regulations). In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The Investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

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

The author of an entry in the source documents should be identifiable.

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

Information collected at unscheduled visits should be documented as described for scheduled visits.

The minimum source documentation requirements for Section 4.1.1, Inclusion Criteria and Section 4.1.2, Exclusion Criteria that specify a need for documented medical history are as follows:

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

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

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

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All eCRF entries, corrections, and alternatives must be made by the Investigator or authorized

study-site personnel. The Investigator must verify that all data entries in the eCRF are accurate and correct.

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

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

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

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

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

17.6. Data Quality Assurance/Quality Control

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

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

17.7. Record Retention

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

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

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

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

17.8. Monitoring

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

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

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

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

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

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed with the last follow-up assessment at Week 176 for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject visit at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

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

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

Reasons for the early closure of a study site by the sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the Investigator
- Discontinuation of further study agent development

17.10. On-site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The Investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

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

17.11. Use of Information and Publication

All information, including but not limited to information regarding ustekinumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the Investigator and not previously published, and any data, including biomarker research data, generated as a result of

this study, are considered confidential and remain the sole property of the sponsor. The Investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

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

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating Investigator for the study. Results of biomarker analyses performed after the Clinical Study Report has been issued will be summarized in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the Investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the Investigator. The Investigator has the right to publish study site-specific data after the primary data are published. If an Investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the Investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the Investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, Investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

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ATTACHMENTS

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Attachment 1: SLICC Classification Criteria

Clinical and Immunological Criteria Used in the SLICC Classification Criteria*+	
Clinical Criteria	**Specific Criteria**
1. Acute Cutaneous Lupus including lupus malar rash (do not count if malar discoid)	• Bullous lupus • Toxic epidermal necrolysis variant of SLE • Maculopapular lupus rash • Photosensitive lupus rash (*in absence of dermatomyositis*) • Subacute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)
2. Chronic cutaneous lupus including classical discoid rash	• Localized (above the neck) • Generalized (above and below the neck) • Hypertrophic (verrucous) lupus • Lupus panniculitis (profundus) • Mucosal lupus • Lupus erythematosus tumidus • Chilblains lupus • Discoid lupus / lichen planus overlap
3. Oral ulcers: palate	• Buccal • Tongue • Nasal *In the absence of other causes such as vasculitis, Behcets, infection (herpes), inflammatory bowel disease, reactive arthritis, and acidic foods*
4. Non-scarring alopecia (diffuse thinning or hair fragility with visible broken hairs)	*In the absence of other causes such as alopecia areata, drugs, iron deficiency and androgenic alopecia*
5. Synovitis involving two or more joints	Characterized by swelling or effusion OR tenderness in 2 or more joints and thirty minutes or more of morning stiffness
6. Serositis	• Typical pleurisy for more than 1 day o Or pleural effusions o Or pleural rub • Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day o Or pericardial effusion o Or pericardial rub o Or pericarditis by ECG *In the absence of other causes such as infection, uremia and Dressler's pericarditis*
7. Renal	• Urine protein/creatinine (or 24-hour urine protein) representing 500 mg of protein/24 hour, **or** • Red blood cell casts

Clinical and Immunological Criteria Used in the SLICC Classification Criteria*+	
8. Neurologic	• Seizures • Psychosis • Mononeuritis multiplex (*in the absence of other known causes such as primary vasculitis*) • Myelitis • Peripheral or cranial neuropathy (*in the absence of other known causes such as primary vasculitis, infection and diabetes mellitus*) • Acute confusional state (*in the absence of other causes including toxic-metabolic, uremia, drugs*)
9. Hemolytic anemia	• Presence
10a. Leukopenia (<4000/mm^3 at least once), **or**	*In the absence of other known causes such as Felty's, drugs, and portal hypertension*
10b. Lymphopenia (<1000/mm^3 at least once)	*In the absence of other known causes such as glucocorticoids, drugs, and infection*
11. Thrombocytopenia (<100,000/mm^3 at least once)	*In the absence of other known causes such as drugs, portal hypertension, and TTP*
Immunological Criteria	**Specific Criteria**
1. ANA	above laboratory reference range
2. Anti-dsDNA	above laboratory reference range, except ELISA; twice above laboratory reference range
3. Anti-Smith	• Presence
4. Anti-phospholipid antibody (any shown to right)	• Lupus anticoagulant • False-positive RPR • Medium or high titer anticardiolipin (IgA, IgG or IgM) • Anti-β_2 glycoprotein 1 (IgA, IgG or IgM)
5. Low Complement	• Low C3 • Low C4 • Low CH50
6. Direct Coombs test	*In the absence of hemolytic anemia*

* Criteria are cumulative and do not need to be present concurrently

\+ Petri M, Orbai AM, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012;64(8):2677-2686.

Attachment 2: Tuberculin Skin Testing

Administering the Mantoux Tuberculin Skin Test

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

Interpreting the Tuberculin Skin Test Results

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

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

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

Treatment of Latent Tuberculosis

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

References

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

Attachment 3: Anticipated Events

Anticipated Event

An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.

For the purposes of this study the following events will be considered anticipated events:

- Systemic lupus erythematosus worsening disease activity
- Selected hematologic abnormal laboratory values (CTCAE grade 1 or 2 leukopenia, lymphopenia, neutropenia, anemia, and thrombocytopenia)

Reporting of Anticipated Events

All adverse events will be recorded in the eCRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described under All Adverse Events in Section 12, Adverse Event Reporting. Any anticipated event that meets serious adverse event criteria will be reported to the sponsor as described under Serious Adverse Events in Section 12. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However, if based on an aggregate review it is determined that an anticipated event is possibly related to study agent, the sponsor will report these events in an expedited manner.

Anticipated Event Analysis Committee)

An Anticipated Event Analysis Committee (AAC) will be established to perform reviews of prespecified anticipated events at an aggregate level. The AAC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The AAC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study agent.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan (ASMP).

Attachment 4: Hepatitis B Virus (HBV) Screening with HBV DNA Testing

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

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

For subjects who **are not eligible for this study due to HBV test results**, consultation with a physician with expertise in the treatment of hepatitis B virus infection is recommended.

Eligibility based on hepatitis B virus test results			
	Hepatitis B test result		
Action	**Hepatitis B surface antigen (HBsAg)**	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc total)**
Include	—	—	—
	—	+	—
	—	+	+
Exclude	+	— *or* +	— *or* +
Require testing for presence HBV DNA*	—	—	+
* If HBV DNA is detectable, exclude from the clinical study. If HBV DNA testing cannot be performed, or there is evidence of chronic liver disease, exclude from the clinical study.			

Attachment 5: Medical Device Incidents: Definition and Procedures for Recording

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 14.1.2).

Medical Device Incident Definition

- A medical device incident is any malfunction or deterioration in the characteristics or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject/user/other person or to a serious deterioration in his/her state of health.
- Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- An **incident** associated with a device happened.

  AND

- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of Incidents

- A subject, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.
- A subject's study agent administration is interrupted or compromised by a medical device failure.
- A misdiagnosis due to medical device failure leads to inappropriate treatment.
- A subject's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

- Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the Investigator's normal clinical practice, and on the appropriate form of the eCRF.
- For incidents fulfilling the definition of an adverse event or a serious adverse event, the appropriate Adverse Event/Serious Adverse Event eCRF page will be completed.

- The eCRF will be completed as thoroughly as possible and signed by the Investigator before transmittal to the sponsor or designee.
- It is very important that the Investigator provides his/her assessment of causality (relationship to the medical device provided by the sponsor) at the time of the initial adverse event or serious adverse event report and describes any corrective or remedial actions taken to prevent recurrence of the incident.
- A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

INVESTIGATOR AGREEMENT

STELARA® (ustekinumab)
Clinical Protocol CNTO1275SLE3001 Amendment 2

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Philippe Szapary, MD, MSCE

Institution: Janssen Research & Development

Signature: PPD Date: 23-JAN-2019
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Approved, Date: 23 January 2019

Janssen Research & Development *

Clinical Protocol

COVID-19 Appendix

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

Protocol CNTO1275SLE3001; Phase 3

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 Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

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

Status: Approved
Date: 23 April 2020
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-RIM-37731, 1.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL CNTO1275SLE3001

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

COVID-19 APPENDIX

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by subjects and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study-related subject management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government guidelines or requirements or the clinical judgement of the investigator to protect the health and well-being of subjects and site staff. If, at any time, a subject's safety is considered to be at unacceptable risk, study agent will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, subjects will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Subjects will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for subjects on study agent, including follow up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation between the subject and investigator, and with the agreement of the sponsor (see below).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a subject has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study agent and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

ADDITIONAL ELEMENTS, WHERE APPLICABLE:

- Certain protocol-mandated visits to the study site may not be possible during the COVID-19 outbreak. Therefore, temporary measures may be implemented if considered appropriate by the sponsor and investigator to maintain continuity of subject care and study integrity. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures:

    - remote (eg, by phone / telemedicine) or in-person, off-site (eg, in-home) interactions between site staff (or designees) and subjects for study procedures e.g. those related to safety monitoring / efficacy evaluation / study agent storage and administration (including training where pertinent)

    - procurement of study agent by subjects (or designee) or shipment of study agent from the study site directly to subjects for at home administration (including the potential for self-administration of study agent)

    - laboratory assessments using a suitably accredited local laboratory; for selected measures (eg, urine pregnancy), home testing may be employed

    - other procedures, eg, imaging, may be conducted at an appropriate facility

- Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study agent and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).

    - other relevant study data elements impacted by the pandemic should also be documented / labeled as "COVID-19-related" in CRFs and / or other study systems, as directed by detailed sponsor guidance. These may include missed / delayed / modified study visits / assessments / dosing, and instances where temporary measures such as those above are implemented.

- The sponsor will evaluate the totality of impact of COVID-19 on collection of key study data and additional data analyses will be outlined in study SAP(s).

- Exclusion: a potential subject with the following features will be excluded from participating in the study protocol:

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

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

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

  AND

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

- NOTES on COVID-related exclusion:

  1. If a subject is excluded due to recent COVID-19-related features, the reason for screen failure should be documented in the case report form under the exclusion criterion of having a condition for which participation would not be in the subject's interest or could confound study assessments.

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

- Precaution: for those who may carry a higher risk for severe COVID-19 illness (eg, those aged over 65 years), follow guidance from local health authorities when weighing the potential benefits and risks of enrolling in the study, and during participation in the study.

INVESTIGATOR AGREEMENT

COVID-19 Appendix
STELARA® (ustekinumab) Clinical Protocol CNTO1275SLE3001

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study agent, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Elizabeth Hsia, MD, MSCE

Institution: Janssen Research & Development

Signature: ELIZABETH HSIA Digitally signed by ELIZABETH HSIA DN: c=US, o=JNJ, ou=Subscribers, 0.9.2342.19200300.100.1.1=333795, cn=ELIZABETH HSIA Reason: I am approving this document. Date: 2020.04.23 16:03:41 -04'00' Date: _____
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Status: Approved, Date: 23 April 2020