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Janssen Research & Development*

Clinical Protocol

A Multicenter, Randomized, Double-blind, Placebo-controlled, Proof-of-Concept Study of Ustekinumab in Subjects With Active Systemic Lupus Erythematosus

CNTO1275SLE2001; Phase 2a
AMENDMENT 3

STELARA® (ustekinumab)

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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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TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

Figures

PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	18 December 2014
Amendment 1	19 May 2015
Amendment 2	24 November 2015
Amendment 3	18 January 2017

Amendments below are listed beginning with the most recent amendment.

Amendment INT-3 (18 January 2017)

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 further evaluate the safety and efficacy of long-term ustekinumab administration in subjects with Systemic Lupus Erythematosus (SLE) who are participating in the CNTO1275SLE2001 study extension.

Applicable Section(s)	Description of Change(s)
Rationale: The primary purpose of the amendment is to allow further evaluation of the safety and efficacy of long-term ustekinumab administration in subjects with Systemic Lupus Erythematosus (SLE) who are participating in the CNTO1275SLE2001 study extension.	
Synopsis Exploratory Objectives	• **Safety and efficacy during long-term administration of ustekinumab.** • **Reduction in corticosteroid dosing during long-term administration of ustekinumab.**
Synopsis Overview of Study Design	Database locks (DBLs) will occur at Weeks 24 and ~~56~~ **following the last subject's Week 56 visit, or the final subject's Week 16 safety follow-up visit from the main study**.
Synopsis Overview of Study Design	**The amended study design will continue to provide open-label ustekinumab 90 mg q8w SC administration through Week 104. Subjects will be eligible to continue study treatment through Week 104 if they meet the study inclusion criteria (Section 4.1.3) including:** • **must not have permanently discontinued study treatment on or before their Week 40 visit, and** • **are able to continue q8 week study treatment at approximately 8 weeks (±2 weeks) after their Week 40 visit** **or** • **are able to resume study treatment with no more than 16 weeks (±2 weeks) since their Week 40 visit.** **In addition to the DBL planned following the final subject's Week 56 visit, or the last subject's Week 16 safety follow-up visit from the main study, there will be an additional DBL at the end of the study extension (following Study Extension 16-week safety follow-up visit).**

Applicable Section(s)	Description of Change(s)
Synopsis Dosage and Administration	Every reasonable effort should be made to keep concomitant medications stable at least through Week 28, with some adjustments allowed beyond Week 28 through ~~Week 48~~ **the 8-Week Safety Follow-Up or study extension** as defined in the protocol. **Subjects who are enrolled in the study extension will continue to receive ustekinumab 90 mg SC administration every 8 weeks through Week 104. With the exception of corticosteroids, concomitant medications should be maintained at stable doses through the study extension.** **After Week 40 to 16-Week Safety Follow-Up (Safety Follow-up Phase)** Groups 1 and 2: Subjects ~~will~~ **who do not participate in the study extension are expected to** return for safety follow-up visits at Weeks~~s~~ **44**~~, 48, and 56~~ **and for 8- and 16-weeks safety follow up**. **Study Extension (Week 48/Week 56 through Week 120)** **Subjects who meet the study extension inclusion criteria (Section 4.1.3) will receive an additional 1 year of open label ustekinumab administration for the purpose of expanding the safety experience and maintenance of efficacy in lupus patients exposed to ustekinumab 90 mg q8w. Subjects who continue dosing in the extended study starting at Week 48 or at Week 56 will receive open-label ustekinumab SC dosing through Week 104. If the development of ustekinumab in SLE is terminated, then the study extension will also be discontinued.**
Synopsis Safety Evaluations	Subject diary cards will be used to capture medication changes that occur in between study visits **during the main portion of this study**.
Time and Events Schedule	**Table 1:** Time and Events Schedule **for the Main Study Design (Screening through 8-Week/16-Week Safety Follow-up)**
Time and Events Schedule	**Main Study** Safety Follow-up Phase **8-Week Safety Follow-up** ~~48~~[b] **16-Week Safety Follow-up**/Final Visit[b]
Time and Events Schedule	b. Subjects, who discontinue study agent administrations on or before the Week 40 visit, must return approximately 8 and 16 weeks after last study agent administration for safety follow-up visits ~~(analogous to assessments done at Week 48 and Week 56, respectively)~~. **The 8-week and/or 16-week safety follow-up visits are not required for subjects who continue treatment in the study extension within 8 (±2 weeks) or 16 (±2 weeks) weeks, respectively, of their Week 40 visit (refer to Table 2).**
Time and Events Schedule	c. All assessments **(except for injection-site evaluation)** are to be completed prior to study agent administration, unless otherwise specified.
Time and Events Schedule	**Table 2: Time and Events Schedule in the CNTO1275SLE2001 Study Extension (Week 48/56 through Extension Safety Follow-up)** added**.**

Applicable Section(s)	Description of Change(s)
Section 1.3. Justification for Dosing Regimen	**Although the dosing rationale has not changed, some additional safety and efficacy information has become available from the ustekinumab Phase 3 CD (UNITI) studies which supports the treatment extension planned for this study. These results from the UNITI CD studies are summarized later in this section (Section 1.3).** **In addition, there were also 3 Phase 3 studies in subjects with CD initiated in 2011 that have recently provided additional safety and efficacy data; UNITI-1, UNITI 2, and IM-UNITI. UNITI-1 and UNITI-2 were 8-week induction studies and were identical in design but studied distinct patient populations. UNITI-1 studied subjects who had failed or were intolerant to anti-TNF agents while UNITI-2 studied subjects who had not failed a TNF antagonist but who had failed conventional immunomodulator or steroid therapies. The IM-UNITI study evaluated maintenance treatment for patients enrolled from both UNITI-1 and UNITI-2 studies. The UNITI studies randomized 1,367 subjects to either placebo, 130 mg IV or approximately 6 mg/kg IV. After Week 8 of therapy, subjects in both UNITI-1 and UNITI-2 studies could enter into IM-UNITI, which primarily evaluated two maintenance regimens of 90 mg every 8 or 12 weeks compared to placebo in induction responders. While the IM-UNITI study is still ongoing in the long-term extension phase, the primary results of all 3 studies have been published,[7] and the results supported the approval of ustekinumab in patients with active moderate to severe CD. The approved dose in induction is a single IV weight-based dose approximating 6 mg/kg and the approved maintenance dose is 90 mg either every 8 or 12 weeks depending on the approval region. The results of these studies are particularly relevant to the CNTO1275SLE2001 SLE study in that a similar dose is being evaluated. In addition, similar to the SLE population, about 1/3 of the CD patients enrolled into the UNITI studies were using concomitant immunomodulators (e.g MTX, AZA, 6-MP) and approximately 46% were on concomitant glucocorticoids. The results of these studies are reviewed in detail in the primary publication[7] and the highlights are presented below:** • **In the 2 UNITI induction studies, the primary endpoint and all major secondary endpoints were met for both doses studied including the 6 mg/kg dose.** • **In the IM-UNITI maintenance study, both the 90 mg every 8 or every 12 week regimens were superior to placebo in maintaining response or achieving remission compared to placebo at Week 44.** • **Importantly, the safety profile of both maintenance doses were comparable to placebo over 44 weeks and no new safety signals were identified. The safety profile was similar to that seen in the psoriatic indications.**

Applicable Section(s)	Description of Change(s)
	In summary, **these CD studies support the dosing regimen planned for this proof-of concept SLE study including** body weight-range based IV loading dose approximating 6 mg/kg followed by 90 mg SC q8w ~~will be employed~~ to ensure a high level of systemic exposure of ustekinumab to inhibit **the actions of** IL-12/23 ~~in this proof-of concept study in subjects with active SLE~~. **Open label 90 mg SC q8w ustekinumab dosing will be provided to subjects starting at Week 24 though Week 40. Per the amended study design, subjects who are able to continue q8w study treatment at approximately 8 weeks (±2 weeks) after their Week 40 visit, or are able to resume study treatment with no more than 16 weeks (±2 weeks) since their Week 40 visit will be eligible for continued 90 mg SC q8w ustekinumab treatment through Week 104, followed by an additional 16-week safety follow-up period.**
2.1. Objectives Exploratory Objectives	• **Safety and efficacy during long-term administration of ustekinumab.** • **Reduction in corticosteroid dosing during long-term administration of ustekinumab.**
3. Study Design and Rationale	A complete list describing all efficacy evaluations and endpoints, and which evaluations are included in the composite endpoints is provided in Attachment 1. **The main study is defined from the original protocol as screening through the Main Study 8-week and 16-week safety follow-up visits. Note that the Main Study 8-week and 16-week safety follow-up visits were previously described in the original protocol as the Week 48 and Week 56 visits. However, with this amendment, the Week 48 and Week 56 visits will only be used to describe treatment visits for those subjects who are participating in the study extension. The study extension (applicable to subjects meeting the inclusion criteria) is defined as the Week 48 or Week 56 visits through the Study Extension 16-week safety follow-up visit.**
3.1. Overview of Study Design	Database locks (DBLs) will occur at Weeks 24 and ~~56~~ **after the final subject's Week 56 visit or following the last subject's 16-week safety follow-up visit from the main study.**

Applicable Section(s)	Description of Change(s)
3.1. Overview of Study Design	**The amended study design will continue to provide open-label ustekinumab 90 mg q8w SC administration through Week 104 (study extension). Subjects will be eligible to continue study treatment through Week 104 if they meet the study inclusion criteria (Section 4.1.3):** • **must not have permanently discontinued study treatment on or before their Week 40 visit, and** • **are able to continue q8 week study treatment at approximately 8 weeks (±2 weeks) after their Week 40 visit** **or** • **are able to resume study treatment with no more than 16 weeks (±2 weeks) since their Week 40 visit** **In addition to the DBL planned following the last subject's Week 56 visit or the final 16-week safety follow-up visit from the main study, there will be an additional DBL following the Extension 16-Week Safety Follow-up period.** A diagram of the **main** study design is provided below in Figure 1**, and a diagram of the extended study is provided in Figure 2**.
3.1. Overview of Study Design	Figure 1: Schematic Overview of the **Main** Study **(Screening through 16-Week Safety Follow-Up)**
3.1. Overview of Study Design	Figure 1 updated
3.1. Overview of Study Design	**Figure 2: Schematic Overview Including the Study Extension** added.
4. Subject Population	**The study extension population will be comprised of those subjects who have not permanently discontinued study treatment before or at the Week 40 dose and for whom the investigators judge that there is a potential benefit that outweighs the potential risks to continued ustekinumab treatment.**

Applicable Section(s)	Description of Change(s)
4.1. Inclusion Criteria	**4.1.3. Inclusion Criteria Applicable to All Subjects Entering into the Study Extension (Week 48 or Week 56 visits)** **Any subjects who do not meet the inclusion criteria for the study extension must follow the Time and Events schedule for the main study design (Table 1), and have safety follow-up visits conducted at 8 and 16 weeks following their Week 40 or final study dose**. **1. Subjects must not have permanently discontinued study treatment on or before their Week 40 visit and are able to either continue q8w SC dosing at approximately 8 weeks (±2 weeks) after their Week 40 visit, or are able to resume dosing at Week 56 with no more than 16 weeks (±2 weeks) since their Week 40 visit.** **2. In the judgment of the study investigator, the potential benefit of continuing ustekinumab long-term treatment outweighs the potential risks for the subject.** **3. Each subject must sign a revised informed consent indicating agreement to participate in the extended study.**
4.3. Prohibitions and Restrictions	Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study **(including the study extension)** to be eligible for continued dosing in the study:
6.2. Subcutaneous administration	**<u>After Week 40 to 16-week Safety Follow up (Safety Follow-up Phase)</u>** **Groups 1 and 2:** Subjects ~~will~~ **who do not participate in the study extension are expected** to return for safety follow-up visits at Weeks **44**~~, 48, and 56~~ **and for 8- and 16-weeks safety follow up**. **<u>Study Extension (Week 48/Week 56 through Week 120)</u>** **Subjects who meet the study extension inclusion criteria will receive open-label ustekinumab administration for the purpose of expanding the safety experience and maintenance of efficacy in lupus patients continuously exposed to ustekinumab 90 mg q8w. Subjects who continue dosing in the extended study starting at Week 48 or at Week 56 will receive open-label ustekinumab SC dosing through Week 104. If the development of ustekinumab in SLE is terminated, then the study extension will also be discontinued.**
7. Treatment Compliance.	**Through the Week 32 visit, t**he visit and study agent administration should occur within ± 7 days of the scheduled visit day (relative to Week 0). **Following the Week 32 visit, the study agent administrations are allowed to occur within ±2 weeks of the scheduled visit day (relative to Week 0).**

Applicable Section(s)	Description of Change(s)
8. Concomitant Therapy	Every reasonable effort should be made to keep concomitant medications stable at least through Week 28, and if possible also through ~~Week 48~~ **the main study 8-week safety follow-up or through the study extension (if applicable)**. **With the exception of corticosteroids (see Section 8.3 regarding corticosteroid tapering), all other concomitant medications should be maintained at stable doses throughout the study.**
8. Concomitant Therapy	Subject diary cards will be used to capture changes in subject-administered medications that occur in between study visits **during the main portion of this study**, and these changes must also be recorded in the concomitant therapy section of the eCRF.
8.1. Immunomodulators	Beyond Week 28, immunomodulators should remain as stable as possible through ~~Week 48~~ **the 8-week safety follow-up or through the study extension (if applicable)**, however, dose adjustment is allowed for unacceptable side effects.
8.2 Antimalarial Medications	Stable treatment with hydroxychloroquine, chloroquine, or quinacrine is permitted through ~~Week 48~~ **the 8-week safety follow-up**.
8.3. Corticosteroid Therapy	Unnecessary dose changes are discouraged, and any dose adjustments should be made in increments. Changes in corticosteroids through ~~Week 48~~ **the 8-week safety follow-up or through the study extension (if applicable)** are allowed for medical necessity, but the degree and timing of the adjustment should be carefully considered as this may have an impact on the study results, especially during the period between 12 and 28 weeks.
8.3. Corticosteroid Therapy	Following Week 28, changes in corticosteroid dosing through ~~Week 48~~ **the 8-week safety follow-up** is allowed for medical necessity, but the degree and timing of the adjustment should be carefully considered as this may have an impact on the study.
8.3. Corticosteroid Therapy	**Gradual tapering of oral corticosteroid dosing in the study extension (recommended reductions of no more than 10 to 20% of the original dose per week) is encouraged starting after the Week 48 dose at the discretion of the study investigator. Tapering to the lowest possible maintenance dose of corticosteroids is recommended, including complete weaning off of corticosteroids if possible. It is recommended that subjects should be educated and monitored by study staff for symptoms of steroid deficiency (eg, Addisonian symptoms) during periods of steroid tapering, as appropriate.** **If subjects experience a worsening in their disease activity while tapering corticosteroids, further dose decreases may be suspended, and/or their oral corticosteroid dose may be temporarily increased if deemed necessary by the investigator. For subjects whose corticosteroid taper is interrupted, investigators are encouraged to resume tapering within 4 weeks.** **In the event of increased corticosteroid dosing, it is recommended that the average dose should not be increased above the baseline dose unless medically necessary. Discretion should be used as any corticosteroid increases may render a subject to be considered a treatment or steroid tapering failure. Sustained oral corticosteroid doses of 40 mg/day or higher may result in discontinuation of study agent.**

Applicable Section(s)	Description of Change(s)
8.3. Corticosteroid Therapy	For subjects in the cutaneous lupus substudy, the initiation of, or an increase from baseline in, the use of potent topical corticosteroids, or intra-lesional corticosteroid injections, is not ~~recommended~~ **allowed** and should be avoided through ~~Week 48~~ **the 8-week safety follow-up or the study extension**.
8.4. Nonsteroidal Anti-inflammatory Drugs	~~After Week 28 and through Week 48, A~~ **Minor a**djustments in NSAID therapy are allowed **after Week 28 although it is recommended that the use of any NSAIDS remain as stable as possible, and any notable changes should be recorded**.
8.5. Anti-hypertensive medications	~~and would result in subject being classified at a treatment failure~~. **Subjects should not initiate any new ARB or ACE inhibitor therapy between randomization and Week 28.**
8.6. Topical Medications	Topical medications are permitted; however, topical compounds cannot include a prohibited medication. Topical ointments or creams of cyclosporine A are prohibited **through Week 28**; however ophthalmic use is permitted. Low potency topical steroids are allowed except on day of study visit**. M**edium to high potency topical corticosteroids are disallowed for all subjects through ~~Week 48~~ **the 8-week safety follow-up, and high potency topical corticosteroids are not allowed for subjects enrolled in the study extension**. For subjects in the cutaneous lupus substudy, topical treatment of target lesions should remain stable during the cutaneous lupus substudy period. For 72 hours prior to study visit, topical medications should not be applied **to lesions under evaluation**.
9.1. Study Procedures **9.1.1. Overview**	The total blood volume to be collected from each subject over the course of the **main portion of the** study will be approximately 640 mL. **The total blood volume to be collected in the study extension between Weeks 48 and 120 will be approximately 250 mL.**
9.1. Study Procedures **9.1.3.1. Week 0/Day of Randomization**	Subject's diary card which was distributed during screening will be reviewed at Week 0, and a new card will be provided at each study visit to record medication changes during the subsequent 4 weeks **through the main portion of the study**.
9.1.4. Post-treatment Phase (Follow-Up)	~~**9.1.4 Post-treatment Phase (Follow-Up)**~~ ~~Post-treatment follow-up visits will occur at 8 and 16 weeks following the last dose received at Week 40 (ie, through Week 56). Assessments will be performed as indicated in the Time and Events Schedule (Table 1). The final efficacy and safety assessments will be performed at Week 56.~~ **9.1.5. Study Extension (Week 48/Week 56 through Week 104)** **Subjects who qualify for participation in the study extension through Week 104 will continue ustekinumab 90 mg q8w SC dosing at approximately 8 weeks (±2 weeks) after their Week 40 visit, or resume ustekinumab dosing at Week 56 with no more than 16 weeks (±2 weeks) since their Week 40 visit.**

Applicable Section(s)	Description of Change(s)
9.1.4.2 Subjects Who Permanently Discontinue Study Agent before Week 40	~~**9.1.4.2 Subjects Who Permanently Discontinue Study Agent before Week 40**~~ **9.1.7 Safety Follow-up for Subjects Who Permanently Discontinue Study Agent at or before Week 104** Subjects who permanently discontinue study agent **at or** before Week 40**, or permanently discontinue at or before Week 104 if they are participating in the study extension**, but do not withdraw from study participation, should be followed for approximately 16 weeks (5 half-lives) after the last study agent administration according to the visit schedule and assessments indicated in the **appropriate** Time and Events Schedule**s** (Table 1 **and Table 2**). Follow-up visits should occur approximately 8 weeks and 16 weeks after the last study agent administration. **Subjects who permanently discontinue study agent before or at Week 40 will not be eligible to participate in the study extension.** Telephone contact will be made to determine reasons for study discontinuation for up to 16 weeks after the last dose of study drug, unless the subject ~~has died,~~ is lost to follow-up, or has withdrawn consent. If the information on reason 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 CRF.
9.2.3. Endpoints	4. [redacted] 5. [redacted] 16. The proportion of subjects with meaningful changes in selected SLE medications from Week 12 ~~through Week 48~~ **Main Study 8-week Safety Follow-up Visit/Week 48**. **17. Change in corticosteroid dose from Week 48 through Week 104 for subjects who participate in the study extension.**
9.8. Safety Evaluations	Refer to Section 4.1 for tuberculosis screening criteria. Subject diary cards will be used to capture medication changes that occur in between study visits **through the main portion of this study**.
9.8. Safety Evaluations	The study will include the following evaluations of safety and tolerability according to the time points provided in Table 1 **and Table 2 for the extended study.**
9.8. Safety Evaluations	**Clinical Laboratory Tests** Blood samples for serum chemistry and hematology will be collected according to the Time and Events Schedule (Table 1 **and Table 2 for the extended study**).

Applicable Section(s)	Description of Change(s)
9.8. Safety Evaluations	**Physical Examination** A full body physical examination will be performed pre-treatment and during the study as shown in Table 1 **and Table 2 for the extended study.**
9.9. Sample Collection and Handling	Refer to the Time and Events Schedule (Table 1 **and Table 2 for the extended study**) for the timing and frequency of all sample collections.
10.1. Completion	A subject **who does not enter into the study extension** will be considered to have completed the **main** study if he or she has completed assessments through ~~Week 56~~ **16-week safety follow-up** of the **main** study. **A subject who has enrolled into the study extension will be considered to have completed the main portion of this study if he or she has completed assessments through either the 8-week safety follow-up visit of the main study.** Subjects who prematurely discontinue study treatment for any reason before ~~Week 56~~ **the Week 8 or Week 16 safety follow-up visits (from the main study),** will not be considered to have completed the **main portion of the** study. **A subject who has enrolled into the study extension will be considered to have completed the study extension if he or she has completed assessments through Week 120.**
10.2. Discontinuation of Study Treatment	If a subject's study treatment must be discontinued before **or at** Week 40 **(for subjects who do not participate in the study extension) or before Week 104 (for subjects who do participate in the study extension),** this will not result in automatic withdrawal of the subject from the study and follow-up assessments should be obtained approximately 8 and 16 weeks following the last dose of study agent.
11.3.1. Primary Endpoint Analyses	• ~~Initiation of new ARB or ACE inhibitor therapy after first dose of study agent and before Week 24.~~ **Subjects who were not receiving ARB or ACE inhibitor therapy who then initiated a new ARB or ACE inhibitor therapy between Week 12 and Week 24. Subjects who substitute an ARB or ACE inhibitor for a comparable medication would not be considered treatment failures.**
11.3.4. Efficacy Analyses in the Long-Term Extension	**Long-term evaluations of efficacy including SRI-4, SLEDAI-2K, PGA, reduction in corticosteroid dosing, and evaluations of flare over time will also be performed for those subjects who participate in the study extension.**
11.11. Data Monitoring Committee	**The DMC will no longer be active after the assessment of the primary endpoint in this study.**
REFERENCES	**7. Feagan, BG, Sandborn WJ, Gasink C, et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med. 2016;375(20):1946-1960.**

Amendment INT-2 (24 November 2015)

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 reasons for the amendment are to provide clarification and additional detail regarding 1) subject eligibility and enrollment, 2) use of restricted and prohibited concomitant medications, 3) refine the definition of the primary endpoint, 4) specify conditions under which subjects may undergo retesting at screening, 5) elaborate on the statistical procedures to be used to conduct the interim and planned data analyses, and 6) provide additional information regarding the collection of samples during the Time and Events Schedule.

Applicable Section(s)	Description of Change(s)
Rationale: Clarifications in several sections in the **Synopsis** regarding: how the SLEDAI-2K scoring, and the BILAG A and BILAG B domain scores will be used to assess subject eligibility for randomization; increased medication use after randomization may result in assessment of the subject as a treatment failure; and evaluation of photographs and/or biopsy samples in subjects who consent to participate in the cutaneous lupus substudy.	
Synopsis Overview of Study Design	**Subjects must also demonstrate at least 1 British Isles Lupus Assessment Group (BILAG) A and/or 2 BILAG B domain scores observed during screening.** ~~. and/or Week 0 prior to first administration of study agent.~~ **In addition, subjects must have a clinical SLEDAI-2K score ≥4 (excluding laboratory results) at week 0, prior to randomization.**
Synopsis Subject Population	**Screening for eligible subjects must be performed no more than 6 weeks prior to the randomization visit (Week 0).** **Subjects must also have at least 1 BILAG A and/or 2 BILAG B domain scores observed during screening prior to first administration of study agent.** **In addition, to be eligible for study participation, subjects must have a clinical SLEDAI-2K score ≥4 (excluding laboratory results) for clinical features at Week 0 (prior to randomization), and have received approval for study randomization following review and adjudication of screening lupus assessments by the Sponsor and/or Sponsor-selected independent reviewer(s).** SLE subjects enrolling into the main study with active cutaneous lupus (including subjects with discoid lupus erythematosus, subacute cutaneous lupus erythematosus, **alopecia** or SLE malar rash or other SLE skin lesions characterized by erythema and or scale) will be evaluated using CLASI scoring.
Synopsis Dosage and Administration	If concomitant medications have been adjusted after randomization as allowed per protocol, every effort should be made to return subject back to the baseline (Week 0) dose level by the Week 12 visit**; or increased medication use may render a subject to be considered a treatment failure.**

Applicable Section(s)	Description of Change(s)
Synopsis Cutaneous Lupus Substudy	Subjects who provide consent will be enrolled in the cutaneous lupus substudy evaluating the histology of cutaneous biopsies and/or skin photographs. Biopsy samples (2 samples, 4 mm size) from consenting subjects will be collected prior to dosing at Week 0 and at Week 24 from a single lesion or area of active cutaneous disease. **Photographs and skin biopsies can target a different area of active disease, but the follow-up photographs or biopsies should re-evaluate the same area of active disease as originally assessed at week 0.** Subjects with cutaneous lupus **deemed** unsuitable for biopsy (eg, malar rash or alopecia) can also be enrolled in the substudy, and may be evaluated by photography.
Rationale: Clarification and addition of explanatory footnotes for key data collection time points specified in the **Time and Events Schedule**.	
TIME AND EVENTS SCHEDULE Footnote a.	**a. Screening visit must be performed no more than 6 weeks prior to the randomization visit (Week 0). To be eligible for study participation, subjects must have SLEDAI score ≥4 (excluding laboratory results) for clinical features at Week 0 and have received approval for study randomization following review and adjudication of screening lupus assessments by the Sponsor and/or Sponsor-selected independent reviewer(s).**
Footnote j.	**j. Subjects should be monitored for the occurrence of infusion or injection-site reactions for 30 minutes after administration of the infusion (IV administration) or injection.**
Footnote q.	**q.** These tests will be performed on-site or at local lab(s).
Footnote w.	**w. Biopsies are allowed to occur on the day of randomization or may occur 1 - 2 days prior to randomization and at the Week 24 visit.**
Footnote x.	**x. Photographs do not need to be taken at the same area of active disease as the biopsy; however, follow-up photographs or biopsies should re-evaluate the same area of active disease as originally assessed at week 0.**
Rationale: Clarification of the **Study Design** with regard to use of the BILAG A and BILAG B domain scores at screening; conduct of 2 interim analyses with inclusion of the assessment of variations in placebo effect across regions.	
3.1 Overview of Study Design	In addition, subjects must have at least 1 positive autoantibody test (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 demonstrate at least 1 BILAG A and/or 2 BILAG B domain scores observed during screening.** ~~and/or Week 0 prior to first administration of study agent~~**. In addition, subjects must have a clinical SLEDAI-2K score ≥ 4 (excluding laboratory results) at week 0, prior to randomization.** Interim analyses (IA) will be conducted when approximately 1/3 and 2/3 of subjects reach Week 24. In the first IA, only ~~an assessment of~~ **evidence for** notable efficacy will be ~~performed~~**assessed**. In the second IA, evidence for notable efficacy as well as treatment futility will be analyzed. **Variations in placebo effect across regions will be incorporated into the interim analyses.**
Rationale: Clarification regarding how the SLEDAI-2K score, and the BILAG A and BILAG B domain scores are used to screen the **Subject Population** prior to randomization.	

Applicable Section(s)	Description of Change(s)
4. Subject Population	**Subjects must have at least 1 BILAG A and/or 2 BILAG B domain scores observed during screening.** In addition, subjects must have at least 1 positive autoantibody test (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, **and they must also have a clinical SLEDAI-2K score ≥4 (excluding laboratory results) prior to randomization at week 0.** ~~Subjects must be scored as having at least 1 BILAG A and/or 2 BILAG B domain scores observed during screening.~~ Subjects with cutaneous lupus **deemed** unsuitable for biopsy (eg, malar rash or alopecia) can also be enrolled in the substudy, and may be evaluated by photography.
Rationale: Clarification of **Inclusion Criteria** and how the SLEDAI-2K scoring, and the BILAG A and BILAG B domain scores will be used to assess subject eligibility for randomization; clarifications regarding antimalarial medications and immunodulatory drugs, and table formatting in the SLICC Classification criteria (leukopenia and lymphopenia).	
4.1.1. Inclusion Criteria Applicable to All Subjects Table 2, 10a, 10b	Table 2: Clinical and Immunological Criteria Used in the SLICC Classification Criteria*[23] **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/mm3 at least once)** — ***In the absence of other known causes such as corticosteroids, drugs, and infection***
Criterion 3; bullet 3.	3. Bullet 3—**At least 1 BILAG A and/or 2 BILAG B domain scores observed during screening prior to first administration of study agent.**
Criterion 4.	4. Demonstrate active disease based on SLEDAI-2K score ≥6 observed during screening and assessed approximately 2 to 6 weeks prior to **randomization**. Must also have SLEDAI-2K ≥4 for clinical features (ie, SLEDAI excluding laboratory results) at Week 0 prior to the first administration of study agent.
Criterion 7.	7. If using antimalarials (eg, chloroquine, hydroxychloroquine, **or quinacrine**), subjects must **have used the medication** for ≥8 weeks and **be** on **a** stable dose for at least 6 weeks prior to the first administration of study agent.
Criterion 8.	8. If using ~~immunosuppressive~~**immunomodulatory** drugs (mycophenolate mofetil [MMF]/mycophenolic acid [MPA] ≤2 g/day, azathioprine/6 mercaptopurine (AZA /6 MP) ≤2 mg/kg/day and/or MTX ≤25 mg/wk with concomitant folic acid [recommend ≥5 mg/wk]), subjects must be receiving a stable dose for at least 6 weeks prior to the first administration of study agent.
Rationale: Clarification of **Additional Inclusion Criteria** for subjects who may not be appropriate for biopsy sample collection in the cutaneous lupus substudy.	
4.1.2. Additional Inclusion Criteria for the Cutaneous Lupus Substudy Criterion 4.	4. Subjects with cutaneous lupus **deemed** unsuitable for biopsy (eg, malar rash or alopecia) can also be enrolled in the substudy, and may be evaluated by photography.
Rationale: Clarification of **Exclusion Criteria** for subjects who have active Lyme disease; treatment with B cell depletion therapy; status as an employee of the investigator; cross-reference to restriction on vaccination with BCG; have used or are using certain immunomodulatory therapies at screening; investigational drug or vaccine treatment; lives in an institution on court or authority order.	

Applicable Section(s)	Description of Change(s)
4.2. Exclusion Criteria Criterion 1.	1. Have other inflammatory diseases that might confound the evaluations of efficacy, including but not limited to rheumatoid arthritis (RA), psoriatic arthritis (PsA), RA/lupus overlap, psoriasis or **active** Lyme disease.
Criterion 3.	3. **Have received systemic or topical cream/ointment preparations of cyclosporine A** or other systemic ~~immunosuppressive~~ **immunomodulatory** agents other than those described in the inclusion criteria within the **past 3 months** prior to first administration of study agent (Section 4.1). Corticosteroids are not included in this criterion; **see Sections 4.3 and 8.3 regarding corticosteroids.**
Criterion 4.	4. Have received **a single B cell targeting agent within 3 months prior to first study agent administration;** or received more than 1 previous B cell targeting therapy including belimumab or epratuzamab within 6 months prior to first administration of the study agent**;** or received B cell depleting therapy (eg, rituximab) within 12 months prior to first administration of the study agent or have evidence of continued B cell depletion following such therapy.
Criterion 6.	6. Have received prior ~~immunosuppressive~~**immunomodulatory** biologic therapy for lupus not described in Exclusion Criterion #4 including, but not limited to, tocilizumab, alefacept, efalizumab, natalizumab, abatacept, anakinra, brodalumab, secukinumab, ixekizumab, **inhibitors of TNF, IL-1, IL-6, IL-17, or interferon pathways**, less than 5 half-lives or 3 months, whichever is longer, prior to first administration of the study agent.
Criterion 13.	13. Have received, or are expected to receive, any live virus or bacterial vaccination within 3 months before the first administration of study agent, during the study, or within 3 months after the last administration of study agent. **For BCG vaccination criterion, see Exclusion Criterion 10 and Prohibition/Restriction Criterion 8.**
Criterion 30.	30. Has received an investigational drug **that is not previously defined in other exclusion criteria** (including investigational vaccines **or other medications specified in section 4.3, prohibition/restriction number 3**) within 5 half-lives or 3 months, whichever is longer ~~**(eg, thalidomide and lenalidomide)**~~, or used an invasive investigational medical device within 3 months before the planned first dose of study drug, or is currently enrolled in an interventional study.
Criterion 36.	36. Subject is an employee of the investigator or study site **(i.e. 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.
Criterion 37.	37. **Lives in an institution on court or authority order, unless permitted by local regulations.**

Rationale: Additions to the list of **Prohibitions and Restrictions** (medications) that must not be used by subjects during the study.

Applicable Section(s)	Description of Change(s)
4.3. Prohibitions and Restrictions	
Prohibition and Restriction 3.	3. Use of additional immunosuppressants or immunomodulators, other than those explicitly allowed in the inclusion/exclusion criteria, are prohibited including but not limited to the following:
Bullet 11	• **Cyclosporine A (oral or topical ointment/cream preparations)**
Bullet 12	• **Tacrolimus or picrolimus, oral or topical preparations**
Bullet 14	• **Thalidomide or lenalidomide**
Bullet 15	• **Dapsone**
Bullet 16	• **Adrenocorticotropic hormone (ACTH) by injection**
Prohibition and Restriction 4.	4. **Use of cytotoxic drugs is prohibited** including, but not limited to, cyclophosphamide, chlorambucil, nitrogen mustard, or other alkylating agents.
Prohibition and Restriction 5.	5. Multiple administrations of high doses of corticosteroids**, and initiation of medium or high potency topical corticosteroids,** are prohibited during the study as defined **in Section 8.3.**
Prohibition and Restriction 6.	6. **The initiation of a new permitted ~~immunosuppressive~~immunomodulatory agent (MTX, azathioprine, 6-mercaptopurine, mycophenolate mofetil/mycophenolic acid) in addition to an ongoing ~~immunosuppressive~~immunomodulatory therapy is prohibited.**
Rationale: Clarification of **Concomitant Therapy** restrictions for subjects who may be receiving treatment with immunomodulators, antimalarials, or corticosteroids (topical or injection) during screening through specified study time points.	
8. Concomitant Therapy	If concomitant medications have been adjusted after randomization as allowed per protocol, every effort should be made to return subject back to the baseline (Week 0) dose level by the Week 12 visit**; or increased medication use (relative to baseline) may render a subject to be considered a treatment failure.**
8.1. Immunomodulators	~~However, immunomodulator dose increases will generally not lead to the discontinuation of study agent administration or termination of study participation.~~ **Permanent discontinuation of the study treatment must be considered for subjects receiving an increase (relative to baseline) in their immunomodulator dose.**
8.2. Antimalarial Medications	Stable treatment with hydroxychloroquine, chloroquine**, or quinacrine** is permitted through Week 48. Beyond Week 28, it is permitted to introduce or adjust dosing of antimalarials. **Antimalarials produced by a licensed compounding pharmacy (eg, quinacrine) in the country of administration and using pharmacaceutical grade components are allowed.**
8.3. Corticosteroid Therapy	
Oral Corticosteriods*	***Rectal administration of corticosteroids, if necessary, should be short-term and using topical preparations.**

Applicable Section(s)	Description of Change(s)
Epidural, Intravenous, Intramuscular, Intra-articular, and Intra-lesional Corticosteroids	Epidural, IV, IM, IA, or intra-lesional administration of corticosteroids is strongly discouraged within 4 weeks prior to the first administration of study agent and is not allowed for the treatment of SLE through Week 28. **Drugs that induce release of endogenous steroids such as ACTH administered by injection are not allowed within 3 months prior to the first administration of study agent and throughout the study.**
Corticosteroid Use in Cutaneous Lupus Substudy	For subjects in the cutaneous lupus substudy, **initiation of medium to high potency topical corticosteroids, or an increase from baseline in the use of medium to high potency topical corticosteroids**, or intra-lesional corticosteroid injections **should** be avoided through Week 48.
8.6 Topical Medications	Topical medications are permitted; however, topical compounds cannot include a prohibited medication. **Topical ointments or creams of cyclosporine A are prohibited; however, ophthalmic use is permitted**.
Rationale: Clarification of conditions under which **Retesting** of subjects for screening laboratory test(s) will bepermitted, and further definition of the SLEDAI-2K score as a composite endpoint and the SRI-4 response endpoint based on various efficacy measures.	
9.1.2.2. Retesting	If a subject has signed the ICF and failed to meet at least 1 entry requirement, a one-time retest of screening laboratory test(s) ~~analyzed by the central laboratory~~ will be allowed in the event of suspected error in sample collection or analysis performance, or a study entry procedure may be repeated once during the screening period if needed. **A request to use a local test to replace a central lab test should be discussed with the medical monitor prior to retesting.** Exceptions to this are positive QuantiFERON®-TB Gold**, 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.**
Rationale: To incorporate the updated versions of the Attachments illustrating the **SLEDAI-2K** and **S2K RI-50** scoring assessments; define values to be used in the assessment of the composite endpoint, **SRI-4**.	
9.2.1.1. SLEDAI-2K and S2K RI-50	**At screening (Attachment 5)**, 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.[31] At baseline **(Attachment 6)**, the features assessed in the SLEDAI-2K are used for comparison to the S2K RI-50 index described below. The SLEDAI-2K has been adapted and developed into the SLEDAI-2K Responder Index (S2K RI-50 [Follow-up], **Attachment 7**)[33], a measure that can document partial improvement in the 24 disease features between SLEDAI-2K assessments.[32]
9.2.2.1. SRI-4	Systemic Lupus Erythematosus Disease Activity Index 2000 SRI-4 response is defined as a **composite endpoint requiring at least a 4 point reduction in SLEDAI 2K** score **(Section 9.2.1.1)**, no worsening (**<10 mm** increase) from baseline in the Physician's Global Assessment of Disease Activity score (PGA) (Section 9.2.1.4), **and no new BILAG Domain A and no more than 1 new BILAG Domain B scores (Section 9.2.1.2)**.[9] SRI-5 and SRI-6 are similarly defined with response requiring a ≥5 point reduction or ≥6 point reduction in SLEDAI 2K, respectively.
Rationale: Clarification of how and when **photographs and biopsy samples** should be collected for exploratory assessments and maintenance of subject confidentiality.	

Applicable Section(s)	Description of Change(s)
9.7 Cutaneous Lupus Substudy	Independent of cutaneous biopsy collection, subjects who participate in the cutaneous lupus substudy will be requested to provide consent for photographs to be collected from an identified cutaneous lesion or an area of active disease. Consenting subjects with cutaneous lupus unsuitable for biopsy (eg, malar rash or alopecia) may be evaluated by photography. The photographs are for exploratory purposes only. The photographs will be used to assist in a qualitative evaluation of clinical response. **The photographs and skin biopsies can target a different area of active disease, but the follow-up photographs or biopsies should re-evaluate the same area of active disease as originally assessed at week 0.** 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.
Rationale: Clarification on when study treatment should be **withheld** or **permanently discontinued** depending on the type of infection a subject has developed and whether it resolves or not; clarification **on urinalysis** for laboratory tests. Urine analyses will be required for all subjects, not only subjects with a history of nephritis or if the primary investigator suspects nephritis may be present.	
9.8 Safety Evaluations Infections	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 treatment must be considered. **Treatment must be permanently discontinued for subjects who develop an opportunistic infection.** 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 no symptoms of infection, may continue study administration after discussion with the study Sponsor.
Clinical Laboratory Tests	The investigator must review the laboratory report immediately upon availability, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. Coomb's direct test, **urine dipstick, urine sediment microscopy** and urine pregnancy test will be performed by site staff or the local laboratory. • Urine Analyses – Fresh spot urine • **Urinalysis using urine dipstick. Urine sample will be further analyzed at Central laboratory.**
Rationale: Clarification of specific **criteria requiring permanent discontinuation** of study treatment, as well as **criteria whereby study treatment discontinuation must be considered**.	

Applicable Section(s)	Description of Change(s)
10.2. Discontinuation of Study Treatment	A subject's study treatment **must be permanently** discontinued if any of the following occur:
Criterion 3.	3. Pregnancy **or planning to become pregnant** within the study period or within 16 weeks after the last study agent injection.
Criterion 4.	4. **The initiation of prohibited medications or treatments (as per Sections 4.3).**
Criterion 9.	9. **Significant worsening of SLE disease activity from baseline or having high disease activity for 2 or more consecutive visits starting at Week 16 based on overall clinical assessments; or if a subject requires the addition of a new immunomodulator to the existing treatment regimen after Week 16.**
Concluding paragraph.	**In addition, permanent discontinuation of study agent treatment must be considered for subjects who:** • **Receive an increase (relative to baseline) in their immunomodulator dose.** • **Develop any of the following adverse events that are reported as serious or severe: study agent infusion reaction, injection-site reaction, or infection.**
Rationale: Clarification of the **statistical procedures** to be used for sample size determination, interim and planned data analyses of the primary and major secondary endpoints, and other efficacy analyses during the study.	
11.2. Sample Size Determination	The sample size calculation is based upon the primary endpoint, proportion of SRI-4 responders at Week 24. Approximately 60 subjects treated with ustekinumab and approximately 40 subjects with placebo is projected to give approximately 80% power to detect a significant difference in response rate compared with placebo (assume 35% and 60% response rates in placebo and ustekinumab respectively, which translates to 25% absolute increase over placebo or an odds ratio of 2.79) with an alpha level of 0.1. The assumption of a 35% responder rate for placebo is based upon a previous study in which a similar SLE population was treated.[34] **Recent studies have shown very high placebo rates in certain regions, thus it is possible that the power for the study could be reduced depending on enrollment and patient assessments conducted in specific regions.**[14]
11.3.1 Primary Endpoint Analysis	**Subgroup analysis based on region will 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 will be presented. Details will be outlined in the SAP.**
11.3.2. Major Secondary Analyses	• The proportion of subjects with BICLA response at Week 24. ~~The BICLA response will be analyzed as defined in the SAP.~~ Continuous responses will be analyzed using an analysis of covariance model with treatment group as a fixed factor and baseline stratifications **(eg, regions)** as a covariate.
11.3.3. Other Planned Efficacy Analyses	Continuous responses will be analyzed using an analysis of covariance model with treatment group as a fixed factor and baseline stratifications (**eg, regions**) as a covariate.
11.4. Interim Analyses	Interim analyses (IA) will be conducted when approximately 1/3 and 2/3 of subjects reach Week 24. **In the first IA, only evidence for notable efficacy will be assessed. In the second IA, evidence for notable efficacy as well as treatment futility will be analyzed. Variations in placebo effect across regions will be incorporated into the interim analyses.** Details concerning the IAs are described in the IA Statistical Analysis Plan.
Rationale: Clarification and inclusion of the **revised definition of the SRI-4 as a composite endpoint** based on other key efficacy measures.	

Applicable Section(s)	Description of Change(s)
ATTACHMENT 1: EFFICACY EVALUATIONS AND ENDPOINTS SRI-4	~~Composite endpoint requiring at least a 4 point reduction in SLEDAI 2K, no worsening (<10 mm increase) from baseline in PGA and no new BILAG Domain A or B scores.~~ **Composite endpoint requiring at least a 4 point reduction in SLEDAI 2K, no worsening (<10 mm increase) from baseline in PGA and no new BILAG Domain A and no more than 1 new BILAG Domain B scores (see Section 9.2.2.1.).**

Amendment INT-1 (19 May 2015)

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 clarify the use of highly effective methods of contraception for subject inclusion and continuation in the study, and correction of minor errors and omissions.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification of highly effective method of contraception	
4.1.1. Inclusion Criterion #10.	Of childbearing potential and practicing a highly effective method of birth control consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: eg, established use of oral, injected or implanted hormonal methods of contraception **associated with inhibition of ovulation**; placement of an intrauterine device or intrauterine system; ~~barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository;~~ male partner sterilization (the vasectomized partner should be the sole partner for that subject); true abstinence (when this is in line with the preferred and usual lifestyle of the subject).
Rationale: Clarification of highly effective method of contraception. Two methods of pregnancy prevention are not required for women using hormonal methods of birth control.	
4.3. Prohibitions and Restrictions, #1.	If a woman is capable of pregnancy, she must remain on a highly effective method of birth control during the study and for 4 months after receiving the last study agent. ~~If she is using hormonal contraceptives, she must use an additional non-hormonal birth control method.~~ The exception to this restriction is if the subject or her male partner is sterilized; this situation does not require birth control. A woman must not 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.
Rationale: An additional exclusion criterion was added	
4.2. Exclusion Criterion, #27.	**Subject has a 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 surgically cured).**
Rationale: An additional exclusion criterion was added.	
4.2. Exclusion Criterion, #36.	**Lives in an institution on court or authority order.**
Rationale: Changed number of categories for region to 'approximately 4'.	
5.1. Procedures for Randomization.	Dynamic central randomization targets to balance the distribution of subjects to achieve the randomization ratio (3:2) at the study level and within the levels of each individual stratification factor: skin biopsy (y/n, when n<16 for y), presence of lupus nephritis (y/n), baseline SLE medications and SLEDAI-2K score (combined factor)*, site, region (approximately ~~3~~ **4** categories), and race (3 categories).

Applicable Section(s)	Description of Change(s)
Rationale: Changed ‘should’ to ‘must’.	
10.2. Discontinuation of Study Treatment.	A subject's study treatment ~~should~~ **must** be permanently discontinued if any of the following occur:
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling corrections were made.

SYNOPSIS

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

STELARA® (ustekinumab) is a fully human G1 kappa monoclonal antibody that binds with high affinity and specificity to the shared p40 subunit of human interleukin (IL)-12 and IL-23 cytokines. The binding of ustekinumab to the IL-12/23p40 subunit blocks the binding of IL-12 or IL-23 to the IL-12Rβ1 receptor on the surface of natural killer and $CD4^+$ T cells, inhibiting IL-12- and IL-23-specific intracellular signaling and subsequent activation and cytokine production. Abnormal regulation of IL-12 and IL-23 has been associated with multiple immune-mediated diseases including Systemic Lupus Erythematosus (SLE). Therefore, inhibition of IL-12 and IL-23 has the potential to be effective in the treatment of SLE.

OBJECTIVE AND HYPOTHESIS

Primary Objective

The primary objective is to evaluate the efficacy of ustekinumab as measured by a reduction in disease activity for subjects with active SLE.

Secondary Objectives

The secondary objectives are to evaluate:

- The safety and tolerability of ustekinumab in subjects with SLE.
- The effect of ustekinumab administration on health-related quality of life in subjects with SLE.
- The effects of ustekinumab on cutaneous manifestations of SLE.
- Pharmacokinetics and immunogenicity of ustekinumab in subjects with SLE.

Exploratory Objective

The exploratory objectives are to evaluate:

- Safety and efficacy during long-term administration of ustekinumab.
- Reduction in corticosteroid dosing during long-term administration of ustekinumab.
- Additional composite clinical endpoints or methods of calculation of clinical response with potential for greater sensitivity to improvement and/or worsening of SLE.
- Biomarkers related to lupus disease (genetic, systemic, and skin-related).

Hypothesis

The hypothesis is that dosing with ustekinumab is significantly superior to placebo as measured by the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) Responder Index (SRI-4) composite measure at Week 24.

OVERVIEW OF STUDY DESIGN

CNTO1275SLE2001 is a Phase 2a, proof-of-concept, multicenter, randomized, double-blind, placebo-controlled study of the efficacy and safety of ustekinumab added to standard of care background in subjects with active SLE. Subjects to be enrolled must have SLE according to Systemic Lupus International Collaborating Clinics (SLICC) criteria and Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score ≥6, despite conventional treatment (eg, immunomodulators, antimalarial drugs, corticosteroids, nonsteroidal anti-inflammatory drugs, anti-hypertensive drugs, and/or topical

medications). 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 medical history. Subjects must also demonstrate at least 1 British Isles Lupus Assessment Group (BILAG) A and/or 2 BILAG B domain scores observed during screening. In addition, subjects must have a clinical SLEDAI-2K score ≥4 (excluding laboratory results) at week 0, prior to randomization.

Approximately 100 subjects will be randomly assigned in a 3:2 ratio to receive either ustekinumab or placebo through Week 24. Following randomization at Week 0, subjects will receive an initial body weight-range based IV dose approximating 6 mg/kg of ustekinumab (ustekinumab 260 mg [weight ≥35 kg to ≤55 kg]; ustekinumab 390 mg [weight >55 kg and ≤85 kg]; ustekinumab 520 mg [weight >85 kg]) followed by 90 mg SC administered every 8 weeks (q8w).

At Week 24, subjects receiving placebo will cross-over and all subjects will receive ustekinumab 90 mg SC at Weeks 24, 32, and 40 followed by safety follow-up through Week 56 in a blinded fashion for 16 weeks (ie, approximately 5 half-lives) after last study agent SC administration.

A placebo comparator (added to standard of care background therapy) will be used through Week 24 for the evaluation of the efficacy and safety of ustekinumab in subjects with SLE. From Week 24 through Week 40, the placebo group will cross-over to receive ustekinumab 90 mg SC q8w. This cross-over design will permit placebo subjects to receive study agent and provide experience with ustekinumab 90 mg SC without the IV loading dose in subjects with SLE. The 40-Week dosing period will be useful to understand the longer term safety and time course of potential clinical response of ustekinumab in the SLE population.

Every reasonable effort should be made to keep concomitant medications stable as defined in the protocol. All concomitant therapies must be recorded throughout the study beginning at entry into screening and any changes must be recorded throughout the study.

All subjects with cutaneous disease will be evaluated using Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) scoring. Additionally, subjects with cutaneous disease who consent to participate in the cutaneous lupus substudy will have other assessments including collection of skin biopsies (optional consent) and/or photographs of a cutaneous lesion or area of active disease (optional consent). There will not be any restrictions on the number of subjects with cutaneous disease who can enroll into either the main study or the cutaneous lupus substudy.

Interim analyses (IA) will be conducted when approximately 1/3 and 2/3 of subjects reach Week 24. In the first IA, only an assessment of notable efficacy will be performed. In the second IA, evidence for notable efficacy as well as treatment futility will be analyzed. Database locks (DBLs) will occur at Weeks 24 and following the last subject's Week 56 visit, or the final subject's Week 16 safety follow-up visit from the main study. In addition, an independent data monitoring committee (DMC) will review interim safety data periodically including a formal review when approximately 1/3 and 2/3 of subjects reach Week 24, as well as at the Week 24 DBL. The DMC will make a recommendation to the Sponsor committee whether the study should be stopped for futility or for safety concerns or if data meet prespecified criteria demonstrating notable efficacy. The content of the summaries, the DMC role and responsibilities, and the general procedures (including communications) will be defined in the DMC charter.

The amended study design will continue to provide open-label ustekinumab 90 mg q8w SC administration through Week 104. Subjects will be eligible to continue study treatment through Week 104 if they meet the study inclusion criteria (Section 4.1.3) including:

- must not have permanently discontinued study treatment on or before their Week 40 visit, and

- are able to continue q8 week study treatment at approximately 8 weeks (±2 weeks) after their Week 40 visit

  or

- are able to resume study treatment with no more than 16 weeks (±2 weeks) since their Week 40 visit.

In addition to the DBL planned after the final subject's Week 56 visit, or after the last subject's Week 16 safety follow-up visit from the main study, there will be an additional DBL at the end of the study extension (following Study Extension 16-week safety follow-up visit).

SUBJECT POPULATION

Screening for eligible subjects must be performed no more than 6 weeks prior to the randomization visit (Week 0). The target study population is subjects with SLE according to SLICC criteria and SLEDAI-2K score ≥6, despite conventional treatment (eg, immunomodulators, antimalarial drugs, corticosteroids, nonsteroidal anti-inflammatory drugs, anti-hypertensive drugs, and/or topical medications). In addition, subjects must have at least 1 positive autoantibody test (ANA, anti-dsDNA antibodies, and/or anti-Smith antibodies) observed during screening, as well as a well-documented positive autoantibody test in medical history. Subjects must also have at least 1 BILAG A and/or 2 BILAG B domain scores observed during screening prior to first administration of study agent.

In addition, to be eligible for study participation, subjects must have a clinical SLEDAI-2K score ≥4 (excluding laboratory results) for clinical features at Week 0 (prior to randomization) and have received approval for study randomization following review and adjudication of screening lupus assessments by the Sponsor and/or Sponsor-selected independent reviewer(s).

SLE subjects enrolling into the main study with active cutaneous lupus (including subjects with discoid lupus erythematosus, subacute cutaneous lupus erythematosus, alopecia or SLE malar rash or other SLE skin lesions characterized by erythema and or scale) will be evaluated using CLASI scoring. In addition, subjects who provide consent will be enrolled in the cutaneous lupus substudy evaluating the histology of cutaneous biopsies and/or skin photographs. Subjects participating in the cutaneous lupus substudy are not required to undergo biopsies, and may allow only photographs to document changes in an identified lesion or area of active disease.

DOSAGE AND ADMINISTRATION

All subjects will receive a body weight range-based IV administration of study agent (placebo or ustekinumab) at Week 0 and then SC administration of placebo or ustekinumab at Weeks 8 and 16, followed by all subjects receiving ustekinumab dosing at Weeks 24, 32, and 40. Every reasonable effort should be made to keep concomitant medications stable at least through Week 28, with some adjustments allowed beyond Week 28 through the 8-Week Safety Follow-Up or study extension as defined in the protocol. A concomitant medication may be reduced or medication temporarily discontinued because of abnormal laboratory values, side effects, 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. If concomitant medications have been adjusted after randomization as allowed per protocol, every effort should be made to return subject back to the baseline (Week 0) dose level by the Week 12 visit; or increased medication use may render a subject to be considered a treatment failure.

Subjects who are enrolled in the study extension will continue to receive ustekinumab 90 mg SC administration every 8 weeks through Week 104. With the exception of corticosteroids, concomitant medications should be maintained at stable doses through the study extension.

Week 0 up to Week 24 (Blinded Study Agent Administration Phase)

Group 1: Subjects will receive weight-range based IV dosing of approximately 6 mg/kg of ustekinumab at Week 0 followed by ustekinumab 90 mg SC administrations at Weeks 8 and 16.

Group 2: Subjects will receive weight-range based IV dosing of placebo at Week 0 followed by placebo SC administrations at Weeks 8 and 16.

Week 24 to Week 40 (Cross-over Administration Phase)

Group 1: Subjects will receive an ustekinumab 90 mg SC administration at Week 24 followed by q8w administrations through Week 40.

Group 2: Subjects in the placebo dosing group will cross-over to ustekinumab 90 mg SC administrations at Week 24 followed by q8w administrations through Week 40.

After Week 40 to 16-Week Safety Follow-Up (Safety Follow-up Phase)

Groups 1 and 2: Subjects who do not participate in the study extension are expected to return for safety follow-up visits at Week 44 and for 8- and 16-weeks safety follow up.

Study Extension (Week 48/Week 56 through Week 120)

Subjects who meet the study extension inclusion criteria (Section 4.1.3) will receive an additional 1 year of open label ustekinumab administration for the purpose of expanding the safety experience and maintenance of efficacy in lupus patients exposed to ustekinumab 90 mg q8w. Subjects who continue dosing in the extended study starting at Week 48 or at Week 56 will receive open-label ustekinumab SC dosing through Week 104. If the development of ustekinumab in SLE is terminated, then the study extension will also be discontinued.

EFFICACY EVALUATIONS

The primary efficacy endpoint of this study is to compare the proportion of subjects with a composite SRI-4 response at Week 24 for subjects receiving ustekinumab as compared to placebo treatment.

Efficacy evaluations and patient reported quality of life measures include:

- SLEDAI-2K
- S2K RI-50
- BILAG
- CLASI
- Physician's Global Assessment of Disease Activity
- Patient's Global Assessment of Disease Activity
- Short-form 36 questionnaire
- Fatigue Severity Scale
- Patient's Assessment of Pain

PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

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

[redacted] EVALUATIONS AND SEROLOGIC MARKERS

The collection, preparation, storage and shipment of skin biopsies, blood, serum and urine are detailed in the Laboratory Manual. Biomarkers may include, but are not limited to, inflammatory markers, ribonucleic acid (RNA), cell surface markers, autoantibodies, T cell and B cell repertoire, target specific markers, and other categories of biomarkers potentially involved in the development and the progression of lupus.

Serum Analyses

Serum will be analyzed for levels of specific proteins [redacted]

Skin Biopsy Analyses

Skin biopsies will be utilized for cellular, molecular, and gene expression analyses.

Whole Blood Gene Expression Analyses

Whole blood will be collected from all subjects for RNA, flow cytometry, T cell and B cell repertoire and epigenetics analysis (eg, deoxyribonucleic acid [DNA] methylation).

Serologic Markers

Autoantibodies (eg, ANA, anti-dsDNA, etc.), complement C3 and C4 will be collected as described in the Table of Events (Table 1).

PHARMACOGENOMIC (DNA) EVALUATIONS

DNA samples will be used for research related to this study (CNTO1275SLE2001). Specific genomic testing will be undertaken for consenting subjects (subjects participating in this portion of the study must sign a separate informed consent form. The procedure will involve taking a blood sample that may be analyzed for specific target genes that may play a role in lupus. Any genomic assessments will be performed in strict adherence to current subject confidentiality standards for genetic testing. Refusal to participate in genomics testing will not result in ineligibility for participation in the rest of the clinical study.

CUTANEOUS LUPUS SUBSTUDY

All subjects with cutaneous disease will be evaluated using CLASI scoring. Additionally subjects with cutaneous disease who consent to participate in the cutaneous lupus substudy will have other assessments including collection of skin biopsies (optional consent) and/or photographs of an identified cutaneous lesion or area of active disease (optional consent). There will not be any restrictions on the number of subjects with cutaneous disease who can enroll into either the main study or the cutaneous lupus substudy.

Subjects who provide consent will be enrolled in the cutaneous lupus substudy evaluating the histology of cutaneous biopsies and/or skin photographs. Biopsy samples (2 samples, 4 mm size) from consenting subjects will be collected prior to dosing at Week 0 and at Week 24 from a single lesion or area of active cutaneous disease. Photographs and skin biopsies can target a different area of active disease, but the follow-up photographs or biopsies should re-evaluate the same area of active disease as originally assessed at week 0. Subjects participating in the cutaneous lupus substudy are not required to undergo biopsies, and may allow only photographs to document changes in an identified lesion or area of active

disease. Subjects with cutaneous lupus deemed unsuitable for biopsy (eg, malar rash or alopecia) can also be enrolled in the substudy, and may be evaluated by photography.

Independent of cutaneous biopsy collection, subjects who participate in the cutaneous lupus substudy will be requested to provide consent for photographs to be collected from an identified lesion or area of active disease. The photographs are for exploratory purposes only. The photographs will be used to assist in a qualitative evaluation of clinical response. 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.

SAFETY EVALUATIONS

Safety assessments include vital signs, general physical exam and skin evaluations, adverse events (AE), serious AEs, concomitant medication review, pregnancy testing, infusion reactions, chemistry and hematology laboratory tests, and antibodies to ustekinumab. Chest x-ray and tuberculosis, human immunodeficiency virus, hepatitis B, and hepatitis C testing will be required at time of screening. Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until a clinically stable endpoint is reached. Subject diary cards will be used to capture medication changes that occur in between study visits during the main portion of this study. Safety data collected up to 16 weeks after the final administration of study agent will be evaluated.

STATISTICAL METHODS

Sample Size Determination

Approximately 100 subjects will be randomly assigned in a 3:2 ratio to receive either ustekinumab or placebo through Week 24. Approximately sixty subjects treated with ustekinumab and approximately 40 subjects with placebo is projected to give approximately 80% power to detect a significant difference in response rate compared with placebo (assume 35% and 60% response rates in placebo and ustekinumab respectively, which translates to 25% absolute increase over placebo or an odds ratio of 2.79) with an alpha level of 0.1.

Efficacy Analyses

The primary endpoint of this study is the proportion of subjects with a composite measure of SLE disease activity (SLE Responder Index [SRI]-4 response) at Week 24. The primary analysis will be based upon the primary endpoint and will be conducted on the modified intent-to-treat (mITT) population, which includes all randomized subjects who receive at least 1 dose of study agent, have at least 1 measurement prior to the administration, and have at least 1 post-baseline SRI-4 measurement.

Last observation carried forward (LOCF) procedure will be used to impute the missing SRI-4 component if the subjects have data for at least 1 SRI-4 component at Week 24. If the subjects do not have data for any SRI components at Week 24, the subjects will be considered not to have achieved the SRI-4 response.

In addition, subjects who meet any of a variety of treatment failure criteria, such as receiving a dose of immunomodulator that is higher at Week 24 than at baseline, or initiated prohibited treatment (dose or timing) with corticosteroids, or discontinued study agent due to a lack of efficacy will be considered to have not achieved the primary endpoint, SRI-4 response at Week 24.

Logistic regression, adjusting for baseline stratifications and baseline SLEDAI, will be used to analyze the primary endpoint. The baseline SLEDAI value is defined as the closest non-missing measurement taken prior to the Week 0 infusion. If significant non-normality is observed, appropriate nonparametric tests will be used to evaluate the differences between treatments.

The study will be considered positive if the primary analysis achieves statistical significance at a significance level of 0.1 (2-sided) and ustekinumab shows a positive treatment effect relative to placebo treatment.

Safety Analyses

Safety will be assessed by analyses of the incidence and type of AEs, SAEs, reasonably related AEs, infections, and infusion reactions. Safety assessments will also include analyses of laboratory parameters and change from baseline in laboratory parameters (hematology and chemistry) and incidence of abnormal laboratory parameters (hematology and chemistry).

TIME AND EVENTS SCHEDULE

Table 1: Time and Events Schedule for the Main Study Design (Screening through 8-Week/16-Week Safety Follow-up)

		Blinded Study Agent Administration Phase							Cross-over Administration Phase				Safety Follow-up		
Week	Screening[a]	0	4	8	12	16	20	24	28	32	36	40	44	8-Week Safety Follow-up[b]	16-Week Safety Follow-up/ Final visit[b]
Study Procedures[c]															
Screening/Administrative															
Informed consent	X														
Inclusion/exclusion criteria	X	X[a]													
Medical history and demographics	X														
SLE classification by SLICC criteria	X														
Study Drug Administration															
Randomization		X													
Study agent administration		X[d]		X		X		X		X		X			
Diary card															
Train on diary card and distribute	X														
Collect, review and distribute diary cards		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessments															
Physical examination	X							X						X	X
HIV, HBV, and HCV	X														
QuantiFERON®-TB Gold test	X														
Tuberculin skin test[e]	X														
TB evaluation[f]	X	X		X		X		X		X		X		X	X
Serum pregnancy test[g]	X														
Urine pregnancy test[h]		X		X		X		X		X		X		X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height		X													
Weight	X	X						X							
Chest x-ray[i]	X														
Concomitant therapy	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

Table 1: Time and Events Schedule for the Main Study Design (Screening through 8-Week/16-Week Safety Follow-up)

		Blinded Study Agent Administration Phase							Cross-over Administration Phase				Safety Follow-up		
Week	Screening[a]	0	4	8	12	16	20	24	28	32	36	40	44	8-Week Safety Follow-up[b]	16-Week Safety Follow-up/ Final visit[b]
Study Procedures[c]															
Infusion or injection-site reaction evaluation[j]		X		X		X		X		X		X			
Cutaneous Lupus Substudy Assessments[k]															
Skin biopsy[w]		X						X							
Photograph lesion or area of active disease[x]		X		X				X		X				X	X
Efficacy Assessments[l]															
SLEDAI-2K (S2K RI-50 - Baseline)	X	X[m]													
S2K RI-50 (Follow-up)			X	X	X	X	X	X	X	X	X	X	X	X	X
CLASI[n]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
BILAG	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
Patient's Global Assessments (Pain and Disease Activity)		X	X	X	X	X	X	X	X	X	X	X	X	X	X
SF-36		X		X		X		X				X		X	X
Fatigue Severity Scale		X	X	X		X		X		X		X		X	X
Clinical Laboratory Assessments															
Hematology[o]	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
Coombs direct test[p,q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Labs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-dsDNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Other autoantibodies[r]	X	X						X						X	
Anti-phospholipid antibodies[p]	X	X						X						X	
Ig isotype profile		X						X						X	
Urine Analyses (spot urine)															

Table 1: Time and Events Schedule for the Main Study Design (Screening through 8-Week/16-Week Safety Follow-up)

		Blinded Study Agent Administration Phase							Cross-over Administration Phase				Safety Follow-up		
Week	Screening[a]	0	4	8	12	16	20	24	28	32	36	40	44	8-Week Safety Follow-up[b]	16-Week Safety Follow-up/ Final visit[b]
Study Procedures[c]															
Urinalysis (dipstick, all study subjects)[q]	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		X		X	X
Protein/Creatinine ratio[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Microscopy of urine sediment[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics/Immunogenicity															
Serum ustekinumab concentrations[s,t]		2X[v]	X	X	X	X		X	X	X		X		X	X
Antibodies to study agent[s,t]		X	X	X	X	X		X				X			X
Pharmacogenomics (DNA)[u]															
Whole blood DNA		X													
Biomarkers															
Serum sample	X	X	X	X	X			X	X	X		X		X	X
Whole blood for RNA gene expression	X	X	X		X			X	X			X		X	X
T cell and B cell repertoire		X			X			X						X	
Epigenetics		X			X			X						X	
Flow cytometry[v]		X			X			X						X	

a. Screening visit must be performed no more than 6 weeks prior to the randomization visit (Week 0). To be eligible for study participation, subjects must have SLEDAI score ≥ 4 (excluding laboratory results) for clinical features at Week 0 and have received approval for study randomization following review and adjudication of screening lupus assessments by the Sponsor and/or Sponsor-selected independent reviewer(s).

b. Subjects, who discontinue study agent administrations on or before the Week 40 visit, must return approximately 8 and 16 weeks after last study agent administration for safety follow-up visits. The 8-week and/or 16-week safety follow-up visits are not required for subjects who continue treatment in the study extension within 8 (±2 weeks) or 16 (±2 weeks) weeks, respectively, of their Week 40 visit (refer to Table 2).

c. All assessments (except for injection-site evaluation) are to be completed prior to study agent administration, unless otherwise specified.

d. Intravenous administration of study agent at Week 0, all other doses will be SC.

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

f. If TB is suspected at any time during the study, a chest x-ray (local), and QuantiFERON®-TB Gold test should be performed. A TST is additionally required if the QuantiFERON®-TB Gold test is not registered/approved locally or the TST is mandated by local health authorities.

Table 1: Time and Events Schedule for the Main Study Design (Screening through 8-Week/16-Week Safety Follow-up)

		Blinded Study Agent Administration Phase							Cross-over Administration Phase				Safety Follow-up		
Week	Screening[a]	0	4	8	12	16	20	24	28	32	36	40	44	8-Week Safety Follow-up[b]	16-Week Safety Follow-up/ Final visit[b]
Study Procedures[c]															

g. In addition to the screening evaluation, the pregnancy test may be repeated at any time at the discretion of investigator or subject.
h. May conduct urine pregnancy test more frequently (eg, monthly basis) if required by local regulations.
i. Posterior/anterior and lateral views must be taken within 3 months prior to the first administration of study agent for TB detection.
j. Subjects should be monitored for the occurrence of infusion or injection-site reactions for 30 minutes after the infusion (IV administration) or injection.
k. Only for subjects who consented to participate in the cutaneous lupus substudy for biopsy and/or photograph collection.
l. All visit-specific patient reported outcome assessments should be conducted before any tests, procedures, or other consultations for that visit to prevent influencing subjects' perceptions.
m. Complete SLEDAI-2K (Baseline) will be evaluated during screening and at Week 0, although at Week 0 only the clinical (non- laboratory) features will be considered to confirm eligibility for study enrollment. The photographs and skin biopsies can target a different location of active disease, but the follow-up photographs or biopsies should re-evaluate the same area of active disease as originally assessed at week 0.
n. CLASI scoring will be obtained for all enrolled subjects with cutaneous lupus regardless of enrollment in the cutaneous lupus substudy.
o. Also perform B cell analyses at screening for subjects previously exposed to B cell depleting therapies.
p. If abnormal test result is not obtained at screening or at Week 0, no additional follow-up testing is required. However, additional testing may be performed if needed.
q. These tests will be performed on-site or at local lab(s).
r. Anti-dsDNA should be analyzed at every specified visit. If the other autoantibody tests are negative at both the screening and Week 0 visits, then those autoantibody tests need only be analyzed again at Weeks 24 and 48. However, if the other autoantibodies tests are positive at either screening or Week 0, then they should be analyzed at all visits.
s. 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.
t. At Week 0 visit, 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.
u. Only for subjects who consent to allow genomic analyses.
v. Flow cytometry samples will be analyzed from subjects at selected sites.
w. Biopsies are allowed to occur 1 - 2 days prior to randomization and at the Week 24 visit.
x. Photographs do not need to be taken at the same area of active disease as the biopsy; however, follow-up photographs or biopsies should re-evaluate the same area of active disease as originally assessed at week 0.

Table 2: Time and Events Schedule in the CNTO1275SLE2001 Study Extension (Week 48/56 through Extension Safety Follow-up)

	Study Extension								Extension Safety Follow-up[a]	
Week	Wk 48	Wk 56	Wk 64	Wk 72	Wk 80	Wk 88	Wk 96	Wk 104	Extension 8-Week Safety Follow-up	Extension 16-Week Safety Follow-up/Final Visit
Study Procedures[b]										
Screening/Administrative										
Informed consent[c]	X	X								
Study Drug Administration										
Study agent administration	X[c]	X[c]	X	X	X	X	X	X		
Safety Assessments										
Physical examination	X		X		X			X	X	X
TB evaluation[d]	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[e]	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X
Injection-site reaction evaluation[f]	X	X	X	X	X	X	X	X		
Efficacy Assessments[g]										
S2K RI-50	X			X		X		X	X	
CLASI[h]	X			X		X		X	X	
BILAG	X			X		X		X	X	
Physician's Global Assessment of Disease Activity	X			X		X		X	X	
Patient's Global Assessments (Pain and Disease Activity)	X			X		X		X	X	
SF-36	X			X				X	X	
Fatigue Severity Scale	X			X				X	X	
Clinical Laboratory Assessments										
Hematology[i]	X	X	X	X	X	X	X	X	X	X
C3, C4	X	X	X	X	X	X	X	X	X	X
Coombs direct test[j,k] (as needed)	X				X			X	X	X
Coagulation Labs (as needed) [i, j]	X				X			X	X	X

Table 2: Time and Events Schedule in the CNTO1275SLE2001 Study Extension (Week 48/56 through Extension Safety Follow-up)

	Study Extension								Extension Safety Follow-up[a]	
Week	Wk 48	Wk 56	Wk 64	Wk 72	Wk 80	Wk 88	Wk 96	Wk 104	Extension 8-Week Safety Follow-up	Extension 16-Week Safety Follow-up/Final Visit
Study Procedures[b]										
Chemistry[k]	X	X	X	X	X	X	X	X	X	X
Anti-dsDNA	X	X	X	X	X	X	X	X	X	X
Other autoantibodies[l]	X				X[l]			X		
Anti-phospholipid antibodies[j]	X				X			X		
Ig isotype profile	X							X		
Urine Analyses (spot urine) [i]										
Urinalysis (dipstick, all study subjects)[i, m]	X	X	X	X	X	X	X	X	X	X
Urine sample for biomarkers (all subjects)	X				X			X	X	X
Protein/Creatinine ratio[i]	X	X	X	X	X	X	X	X	X	X
Microscopy of urine sediment[k,m]	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics/Immunogenicity										
Serum ustekinumab concentrations[n]	X				X			X	X	X
Antibodies to study agent[n]	X				X			X	X	X
Biomarkers										
Serum sample	X				X			X	X	X
Whole blood for RNA gene expression	X				X			X	X	X

Table 2: Time and Events Schedule in the CNTO1275SLE2001 Study Extension (Week 48/56 through Extension Safety Follow-up)

	Study Extension								Extension Safety Follow-up[a]	
Week	Wk 48	Wk 56	Wk 64	Wk 72	Wk 80	Wk 88	Wk 96	Wk 104	Extension 8-Week Safety Follow-up	Extension 16-Week Safety Follow-up/Final Visit
Study Procedures[b]										

a. Subjects, who complete all scheduled doses or discontinue study agent administration before the end of the study extension, must return at approximately 8 and 16 weeks after last study agent administration for safety follow-up visits.

b. All assessments (except for injection-site evaluation) are to be completed prior to study agent administration.

c. Prior to dosing in the study extension, subjects must sign a revised ICF indicating agreement to participate in the extended study.

d. 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), and QuantiFERON®-TB Gold test should be performed. A TST is additionally required if the QuantiFERON®-TB Gold test is not registered/approved locally or the TST is mandated by local health authorities.

e. In addition to scheduled urine dipstick testing, a serum or urine pregnancy test may be conducted at any time at the discretion of investigator or subject, or if required by local regulations.

f. Subjects should be monitored for the occurrence of injection-site reactions for 30 minutes after the injection.

g. All visit-specific patient reported outcome assessments should be conducted before any tests, procedures, or other consultations for that visit to prevent influencing subjects' perceptions.

h. CLASI scoring will be obtained for all enrolled subjects who have cutaneous lupus.

i. If clinical concerns or abnormal results from prior visit observed in these assessments, then strong consideration should be given to more frequent testing (at least q4 week assessments) until normalized

j. If history of abnormal test result was observed in main study, then follow scheduled assessments. Additional testing may be performed if needed.

k. These tests will be performed on-site or at local lab(s).

l. If the "other autoantibody" tests were routinely negative prior to Week 48, then those autoantibody tests need only be analyzed annually. However, if the other autoantibodies tests were positive at either screening or Week 0, then they should be analyzed every 6 months as shown.

m. Urine sediment analyses to be performed at study site or local lab if possible. If necessary, with agreement from study sponsor, urine sediment analyses can be conducted at the Central Lab for specific sites that cannot arrange local analyses.

n. 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 pre-dose ustekinumab concentration and antibodies to ustekinumab MUST be collected BEFORE the administration of the study agent.

ABBREVIATIONS

ACE	angiotensin-converting enzyme
AE	adverse event
ANA	antinuclear antibodies
ANCOVA	analysis of covariance
anti-dsDNA	anti-double stranded deoxyribonucleic acid
anti-HBc total	HBV core antibody total
anti-HBs	HBV surface antibody
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
BICLA	BILAG-based Combined Lupus Assessment
BILAG	British Isles Lupus Assessment Group
BLyS	B lymphocyte stimulator, also known as B cell activating factor (BAFF)
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CLE	cutaneous lupus erythematosus
CNS	central nervous system
COX-2	cyclooxygenase-2
CRF	case report form
CD	Crohn's disease
CTCAE	Common Terminology Criteria for Adverse Events
CXCL10	C-X-C motif chemokine 10
DMC	data monitoring committee
DNA	deoxyribonucleic acid
eCRF	electronic case report form
eDC	Electronic Data Capture
EDTA	ethylenediaminetetraacetic acid
ELISA	enzyme-linked immunosorbent assay
FSS	Fatigue Severity Scale
FVP	Final Vialed Product
GCP	Good Clinical Practice
HBsAg	HBV surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IA	interim analyses
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IL	Interleukin
IM	Intramuscular

IP	Investigative Product
IRB	Institutional Review Board
IV	Intravenous
IWRS	interactive web response system
JAK	janus kinase
mITT	modified intent-to-treat
MMF	mycophenolate mofetil
MPA	mycophenolic acid
MTX	Methotrexate
NAbs	neutralizing antibodies
NSAIDs	nonsteroidal anti-inflammatory drugs
PFS	prefilled syringe
PGA	Physician's Global Assessment of Disease Activity
PK	Pharmacokinetic
PQC	product quality complaint
PROs	patient reported outcomes
PsA	psoriatic arthritis
PtGA	Patient's Global Assessment of Disease Activity
q8w	every 8 weeks
RA	rheumatoid arthritis
RNA	ribonucleic acid
RNP	Ribonucleoprotein
S2K RI-50	SLEDAI-2K Responder Index
SAE	serious AE
SAP	statistical analysis plan
SC	Subcutaneous
SF	Short-form
SLE	Systemic Lupus Erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SLICC	Systemic Lupus International Collaborating Clinics
SRI-4	SLE Responder Index
SSA	anti-Sjögren's-syndrome-related antigen A
SSB	anti-Sjögren's-syndrome-related antigen B
TB	Tuberculosis
Th	T helper
TNFα	tumor necrosis factor alpha
ULN	upper limit of normal
VAS	visual analogue scale
WBC	white blood cells

1. INTRODUCTION

STELARA® (ustekinumab) is a fully human G1 kappa monoclonal antibody that binds with high affinity and specificity to the shared p40 subunit of human interleukin (IL)-12 and IL-23 cytokines. The binding of ustekinumab to the IL-12/23p40 subunit blocks the binding of IL-12 or IL-23 to the IL-12Rβ1 receptor on the surface of natural killer and $CD4^+$ T cells, inhibiting IL-12- and IL-23-specific intracellular signaling and subsequent activation and cytokine production. Abnormal regulation of IL-12 and IL-23 has been associated with multiple immune-mediated diseases including systemic lupus erythematosus (SLE). Therefore, inhibition of IL-12 and IL-23 has the potential to be effective in the treatment of SLE.

Systemic lupus erythematosus is a complex, chronic autoimmune disease of unknown etiology that can affect almost any organ system, and which follows a relapsing and remitting disease course. Systemic lupus erythematosus occurs much more often in women than in men, up to 9 times more frequently in some studies, and often appears during the child-bearing years between 15 and 45. This disease is more prevalent in Afro-Caribbean, Asian, or Hispanic populations. In SLE, the immune system attacks the body's cells and tissue, resulting in inflammation and tissue damage which can harm the heart, joints, skin, lungs, blood vessels, liver, kidneys and nervous system. About half of the subjects diagnosed with SLE present with organ-threatening disease, but it can take several years to diagnose subjects 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.[39] The estimated annual incidence of lupus varies from 1.8 to 7.6 cases per 100,000 and the worldwide prevalence ranges from 14 to 172 cases per 100,000 people.[39] Patients with mild disease have mostly skin rashes and joint pain and require little medication; regimens include nonsteroidal anti-inflammatory drugs (NSAIDs), anti-malarials (eg, hydroxychloroquine, chloroquine, or quinacrine) and/or low dose corticosteroids. 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 problems, stroke, neurological complications, vasculitis and cytopenias with associated risks of bleeding or infection. Common treatments for more severe disease include immunomodulatory agents, such as methotrexate (MTX), azathioprine, cyclophosphamide, cyclosporine, high dose corticosteroids, biologic B cell cytotoxic agents or B cell modulators, and other immunomodulators. Patients with serious SLE have a shortening of life expectancy by 10 to 30 years, largely due to the complications of therapy and accelerated atherosclerosis, as well as experiencing a substantial impact of this disease on their quality of life. Existing therapies for SLE are generally either cytotoxic or immunomodulatory, and may have notable safety risks when used over long periods of time. Newer treatments for SLE have provided only modest benefits over standard of care therapy. 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.

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 consent, access to health care, adherence to treatment, education and other comorbidities. Only about 5% of patients who are diagnosed with SLE will demonstrate a spontaneous remission without treatment. A variety of new therapeutic agents are being evaluated for the treatment of subjects with refractory lupus, however to date very few have demonstrated notable clinical efficacy beyond those medications currently considered standard of care for patients with this disease.

In this study, the target population is subjects with SLE according to Systemic Lupus International Collaborating Clinics (SLICC) criteria and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[11] score ≥6, despite conventional treatment (eg, immunomodulators, antimalarial drugs, corticosteroids, NSAIDs, anti-hypertensive drugs, and/or topical medications). 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 medical history. Subjects must also demonstrate at least 1 British Isles Lupus Assessment Group (BILAG)[38] A and/or 2 BILAG B domain scores during screening. In addition, subjects must have a SLEDAI score ≥4 at Week 0 (prior to randomization) for clinical features (excluding laboratory results).This level of disease activity is consistent with prior studies that have investigated an experimental therapy for systemic lupus.[36]

For the most comprehensive nonclinical and clinical information regarding ustekinumab, refer to the latest version of the Investigator's Brochure and Addenda for ustekinumab.

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 approval globally, including countries in North America, Europe, South America, and the Asia-Pacific region, for the treatment of adult patients including those with chronic moderate to severe plaque psoriasis and/or active psoriatic arthritis. Ustekinumab is also being evaluated in a Phase 3 studies for Crohn's disease (CD).

1.2. Overall Rationale for the Study

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

Systemic lupus erythematosus is a complex, immune-mediated inflammatory disorder exhibiting dysregulated B lymphocytes that produce destructive autoantibodies. B cell targeted therapies (eg, belimumab) for SLE, however, have shown only modest clinical results beyond a limited standard of care control,[22] suggesting that additional immune pathways play an important role in SLE pathogenesis. Chronic immune activation in SLE leads to the increased production of inflammatory cytokines that contribute actively to local inflammation and to processes that

mediate tissue damage. Many SLE patients, for example, have a characteristic type I interferon signature observed in their blood cells.[2] Interferon signatures have also been observed to occur more frequently in lupus families and may be a risk factor for development of SLE.[23] Several studies have also reported an elevation of IL-12, IL-6, and IL-23 in both serum and tissues of patients,[4,20,24,26,30,44] suggesting that the inflammatory environment in SLE is prone to induce T helper (Th)1 and Th17 cells. Increased levels of IL-17 in the serum have been observed in SLE patients,[3,31,36,44,45,46] but the correlation of IL-17 levels to disease activity is not strong.[37,46] No direct genetic links have been established in SLE to the IL-12/IL-23/Th17 pathway,[18,28,29] although genome-wide association studies in SLE have identified STAT4, which mediates IL-12 signaling, as a susceptibility gene in both the Caucasian and Asian populations.[12,16] In patients with active SLE, messenger RNA levels of p19, p40, and p35 were significantly higher compared with those in the inactive SLE patients.[14] Targeting IL-12/23p40 with ustekinumab has been shown in 3 separate case reports to be associated with a marked improvement of cutaneous lupus.[5,6,43] Taken together, there is accumulating evidence to demonstrate the importance of the IL-12 and IL-23 cytokine pathways in SLE pathogenesis, warranting further clinical investigation of ustekinumab as an interventional therapy in this disease.

In addition, 2 disease-related groups, the Alliance for Lupus Research and Lupus Research Institute, independently commissioned a scientific review of a large set of commercially available lupus drug candidates, from which ustekinumab was recommended to be evaluated in SLE based on its molecular mechanism, which further supports the scientific rationale for a placebo-controlled clinical study to evaluate the efficacy and safety of ustekinumab in subjects with active SLE.

1.2.1.1. Subgroup of Subjects with Active Cutaneous Manifestations of Systemic Lupus Erythematosus

The above mentioned case reports of patients with refractory cutaneous lupus responding to ustekinumab treatment prompts an evaluation of the effects of ustekinumab on cutaneous lesions. Given the relatively common occurrence of cutaneous manifestations in SLE, the feasibility of repeated punch biopsy and/or photographs of an identified lesion or area of active disease, and the availability of cutaneous lupus erythematosus (CLE)-specific disease assessment tools, this patient population may provide useful data regarding the effects of ustekinumab on SLE and the symptoms of cutaneous disease. All subjects with cutaneous disease will be evaluated using CLASI scoring. Additionally subjects with cutaneous disease who consent to participate in the cutaneous lupus substudy will be requested to provide potential collection of skin biopsies (optional consent) and/or photographs of an identified lesion or area of active disease (optional consent). There are no pre-specified numbers of subjects to be enrolled with cutaneous disease for either the main study or the cutaneous lupus substudy.

1.3. Justification for Dosing Regimen

The dosing regimen for this study was selected based on experience with the use of ustekinumab in the treatment of subjects with moderately to severely active CD (C0743T26, CNTO1275CRD3001, and CNTO1275CRD3002). Both CD and SLE are immune-mediated inflammatory diseases, which are commonly treated with immunomodulators, such as

methotrexate (MTX), azathioprine and corticosteroids, and thus this indication serves as a useful model for risk assessment of ustekinumab in lupus. Although the dosing rationale has not changed, additional safety and efficacy information has become available from the ustekinumab Phase 3 CD (UNITI) studies which supports amending the protocol to further extend treatment with ustekinumab 90 mg SC q8w for an additional year. These results from the UNITI CD studies are summarized later in this section.

Although the dosing rationale has not changed, some additional safety and efficacy information has become available from the ustekinumab Phase 3 CD (UNITI) studies which supports the treatment extension planned for this study. These results from the UNITI CD studies are summarized later in this section (Section 1.3).

In the Phase 2b dose ranging study C0743T26, a single IV ustekinumab dose of 6 mg/kg was the highest loading dose tested in subjects with CD. In this study, the 6 mg/kg IV dose was shown to be effective in inducing clinical response through Week 8 and was well tolerated with a safety profile generally comparable to the other treatment groups. Results from ustekinumab CD studies also suggest that an IV loading dose may provide a rapid onset of clinical response following IL-12 and IL-23 inhibition. In the Phase 3 studies CNTO1275CRD3001 and CNTO1275CRD3002, body weight-range dosing approach (ustekinumab 260 mg [weight ≤55 kg]; ustekinumab 390 mg [weight >55 kg and ≤85 kg]; ustekinumab 520 mg [weight >85 kg]) was used to approximate the IV loading dose of 6 mg/kg. The body weight-range based dosing allows administration of complete vials to patients to simplify dose calculation and reduce the potential for errors in dosing. This weight range dosing is intended to achieve drug exposure similar to that observed with 6 mg/kg weight-adjusted dosing. Thus, in this study, a strategy of IV loading dose based on body weight range at Week 0 will be evaluated to assess the ability of the drug to rapidly reduce the disease activity of SLE without causing significant concern for increased safety risk based on data obtained from previous studies.

The ustekinumab maintenance dosing regimen of 90 mg SC every 8 weeks (q8w) was studied in subjects with CD (C0743T26). The results from C0743T26 study suggest that ustekinumab 90 mg SC q8w was safe and effective in maintaining subjects in clinical remission. The q8w dosing frequency is selected to maintain sufficient ustekinumab exposure to determine if treatment with ustekinumab can provide sustained clinical response. In addition, SC administration is considered more convenient compared with IV administration. A 16-week follow-up period following last ustekinumab study dose was selected to allow more than 5 half-lives for drug elimination and adequate safety follow-up.

In addition, there were also 3 Phase 3 studies in subjects with CD initiated in 2011 that have recently provided additional safety and efficacy data; UNITI-1, UNITI 2, and IM-UNITI. UNITI-1 and UNITI-2 were 8-week induction studies and were identical in design but studied distinct patient populations. UNITI-1 studied subjects who had failed or were intolerant to anti-TNF agents while UNITI-2 studied subjects who had not failed a TNF antagonist but who had failed conventional immunomodulator or steroid therapies. The IM-UNITI study evaluated maintenance treatment for patients enrolled from both UNITI-1 and UNITI-2 studies. The UNITI

studies randomized 1,367 subjects to either placebo, 130 mg IV or approximately 6 mg/kg IV. After Week 8 of therapy, subjects in both UNITI-1 and UNITI-2 studies could enter into IM-UNITI, which primarily evaluated two maintenance regimens of 90 mg every 8 or 12 weeks compared to placebo in induction responders. While the IM-UNITI study is still ongoing in long-term extension phase, the primary results of all 3 studies have been published,[7] and the results supported the approval of ustekinumab in patients with active moderate to severe CD. The approved dose in induction is a single IV weight-based dose approximating 6 mg/kg and the approved maintenance dose is 90 mg either every 8 or 12 weeks depending on the approval region. The results of these studies are particularly relevant to the CNTO1275SLE2001 SLE study in that a similar dose is being evaluated. In addition, similar to the SLE population, about 1/3 of the CD patients enrolled into the UNITI studies were using concomitant immunomodulators (e.g MTX, AZA, 6-MP) and approximately 46% were on concomitant glucocorticoids. The results of these studies are reviewed in detail. in the primary publication[7] and the highlights are presented below:

- In the 2 UNITI induction studies, the primary endpoint and all major secondary endpoints were met for both doses studied including the 6 mg/kg dose.
- In the IM-UNITI maintenance study, both the 90 mg every 8 or every 12 week regimens were superior to placebo in maintaining response or achieving remission compared to placebo at Week 44.
- Importantly, the safety profiles of both maintenance doses were comparable to placebo over 44 weeks and no new safety signals were identified. The safety profile was similar to that seen in the psoriatic indications.

In summary, these CD studies support the dosing regimen planned for this proof-of concept SLE study including body weight-range based IV loading dose approximating 6 mg/kg followed by 90 mg SC q8w to ensure a high level of systemic exposure of ustekinumab to inhibit the actions of IL-12/23.

Open label 90 mg SC q8w ustekinumab dosing will be provided to subjects starting at Week 24 though Week 40. Per the amended study design, subjects who are able to continue q8w study treatment at approximately 8 weeks (±2 weeks) after their Week 40 visit, or are able to resume study treatment with no more than 16 weeks (±2 weeks) since their Week 40 visit will be eligible for continued 90 mg SC q8w ustekinumab treatment through Week 104, followed by an additional 16-week safety follow-up period.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective

The primary objective is to evaluate the efficacy of ustekinumab as measured by a reduction in disease activity for subjects with active SLE.

Secondary Objectives

The secondary objectives are to evaluate:

- The safety and tolerability of ustekinumab in subjects with SLE.
- The effect of ustekinumab administration on health-related quality of life in subjects with SLE.
- The effects of ustekinumab on cutaneous manifestations of SLE.
- Pharmacokinetics and immunogenicity of ustekinumab in subjects with SLE.

Exploratory Objectives

The exploratory objectives are to evaluate:

- Safety and efficacy during long-term administration of ustekinumab.
- Reduction in corticosteroid dosing during long-term administration of ustekinumab.
- Additional composite clinical endpoints or methods for calculation of response with potential for greater sensitivity to improvement and/or worsening of SLE.
- Biomarkers related to lupus disease (genetic, systemic, and skin-related).

2.2. Hypothesis

The hypothesis is that ustekinumab is significantly superior to placebo as measured by the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) Responder Index (SRI-4) composite measure at Week 24.

3. STUDY DESIGN AND RATIONALE

A complete list describing all efficacy evaluations and endpoints, and which evaluations are included in the composite endpoints is provided in Attachment 1. The main study is defined from the original protocol as screening through the Main Study 8-week and 16-week safety follow-up visits. Note that the Main Study 8-week and 16-week safety follow-up visits were previously described in the original protocol as the Week 48 and Week 56 visits. However, with this amendment, the Week 48 and Week 56 visits will only be used to describe treatment visits for those subjects who are participating in the study extension. The study extension (applicable to subjects meeting the inclusion criteria) is defined as the Week 48 or Week 56 visits through the Study Extension 16-week safety follow-up visit.

3.1. Overview of Study Design

CNTO1275SLE2001 is a Phase 2a, proof-of-concept, multicenter, randomized, double-blind, placebo-controlled study of the efficacy and safety of ustekinumab added to standard of care background therapy in subjects with active SLE. Subjects between 18 and 75 years of age must have SLE according to SLICC criteria and SLEDAI-2K score ≥6, despite conventional treatment (eg, immunomodulators, antimalarial drugs, corticosteroids, NSAIDs, anti-hypertensive drugs, and/or topical medications). In addition, subjects must have at least 1 positive autoantibody test

(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 demonstrate at least 1 BILAG A and/or 2 BILAG B domain scores observed during screening**.** In addition, subjects must have a clinical SLEDAI-2K score ≥4 (excluding laboratory results) at week 0, prior to randomization.

Subject randomization will be stratified according to consent for skin biopsy collection (y/n), and other features (eg, presence of lupus nephritis [y/n], baseline SLE medications and SLEDAI score), site/region, and race, or concomitant medications as described in Section 8.

Approximately 100 subjects will be randomly assigned by 3:2 ratio to receive either ustekinumab or placebo through Week 24. Following randomization at Week 0, subjects will receive an initial body weight-range based IV dose approximating 6 mg/kg of ustekinumab (ustekinumab 260 mg [weight ≥35 kg to ≤55 kg]; ustekinumab 390 mg [weight >55 kg and ≤85 kg]; ustekinumab 520 mg [weight >85 kg]) followed by 90 mg SC administered q8w (Section 6). At Week 24, subjects receiving placebo will cross-over and all subjects will receive ustekinumab 90 mg SC at Weeks 24, 32, and 40 followed by safety follow-up through Week 56 in a blinded fashion for 16 weeks (ie, approximately 5 half-lives) after last study agent SC administration.

A placebo comparator (added to standard of care background therapy) will be used through Week 24 for the evaluation of the efficacy and safety of ustekinumab in subjects with SLE. From Week 24 through Week 40, the placebo group will cross-over to ustekinumab 90 mg SC q8w. This cross-over design will permit placebo subjects to receive study agent and provide experience with ustekinumab 90 mg SC without the IV loading dose in subjects with SLE. The 40-Week dosing period will be useful to understand the longer term safety and time course of potential clinical response of ustekinumab in the SLE population.

Every reasonable effort should be made to keep concomitant medications stable as defined in the protocol. All concomitant therapies must be recorded throughout the study beginning at entry into screening and any changes must be recorded throughout the study.

All subjects with cutaneous disease will be evaluated using CLASI scoring. Additionally, subjects with cutaneous disease who consent to participate in the cutaneous lupus substudy will have other assessments including collection of skin biopsies (optional consent) and/or photographs of an identified cutaneous lesion or area of active disease (optional consent). There will not be any restrictions on the number of subjects with cutaneous disease who can enroll into either the main study or the cutaneous lupus substudy.

Interim analyses (IA) will be conducted when approximately 1/3 and 2/3 of subjects reach Week 24. In the first IA, only evidence for notable efficacy will be assessed. In the second IA, evidence for notable efficacy as well as treatment futility will be analyzed. Variations in placebo effect across regions will be incorporated into the interim analyses. Database locks (DBLs) will occur at Weeks 24 and after the final subject's Week 56 visit or following the last subject's 16-week safety follow-up visit from the main study. In addition, an independent data monitoring committee (DMC) will review interim safety data periodically including a formal review when

approximately 1/3 and 2/3 of subjects reach Week 24, as well as at the Week 24 DBL. The DMC will make a recommendation to the Sponsor committee whether the study should be stopped for futility or for safety concerns or if data meet prespecified criteria demonstrating notable efficacy. The content of the summaries, the DMC role and responsibilities, and the general procedures (including communications) will be defined in the DMC charter.

The amended study design will continue to provide open-label ustekinumab 90 mg q8w SC administration through Week 104 (study extension). Subjects will be eligible to continue study treatment through Week 104 if they meet the study inclusion criteria (Section 4.1.3):

- must not have permanently discontinued study treatment on or before their Week 40 visit, and
- are able to continue q8 week study treatment at approximately 8 weeks (±2 weeks) after their Week 40 visit

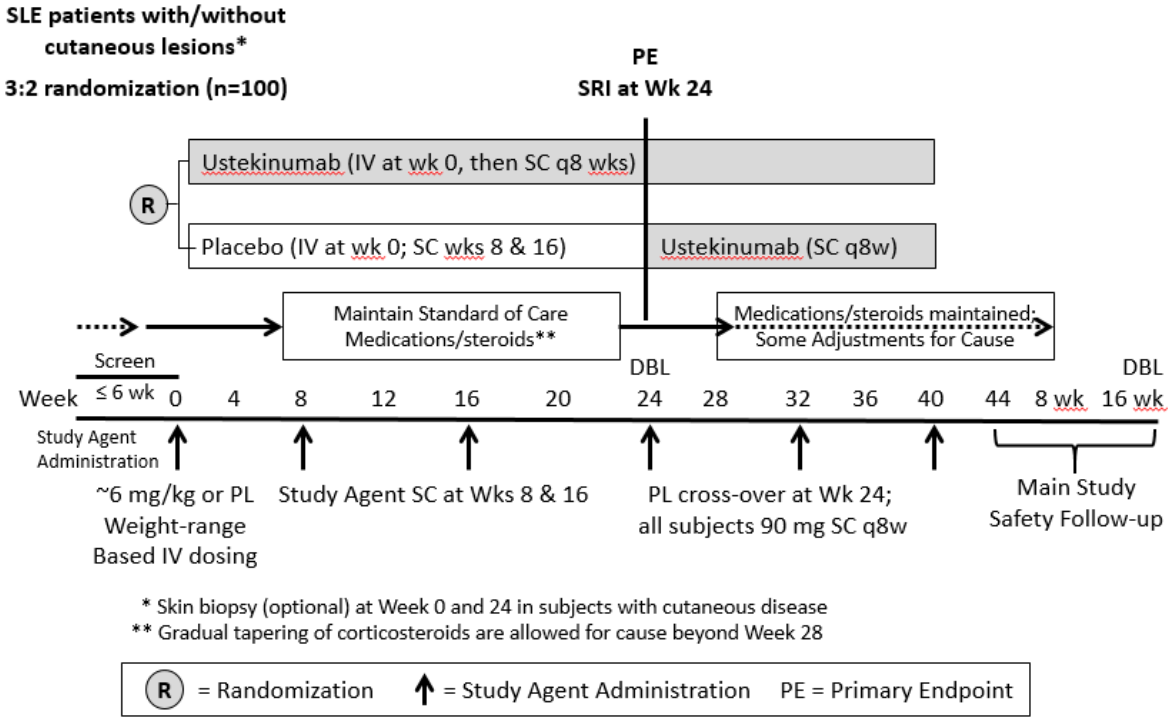
or

- are able to resume study treatment with no more than 16 weeks (±2 weeks) since their Week 40 visit

In addition to the DBL planned following the last subject's Week 56 visit or the final 16-week safety follow-up visit from the main study, there will be an additional DBL following the Extension 16-Week Safety Follow-up period.

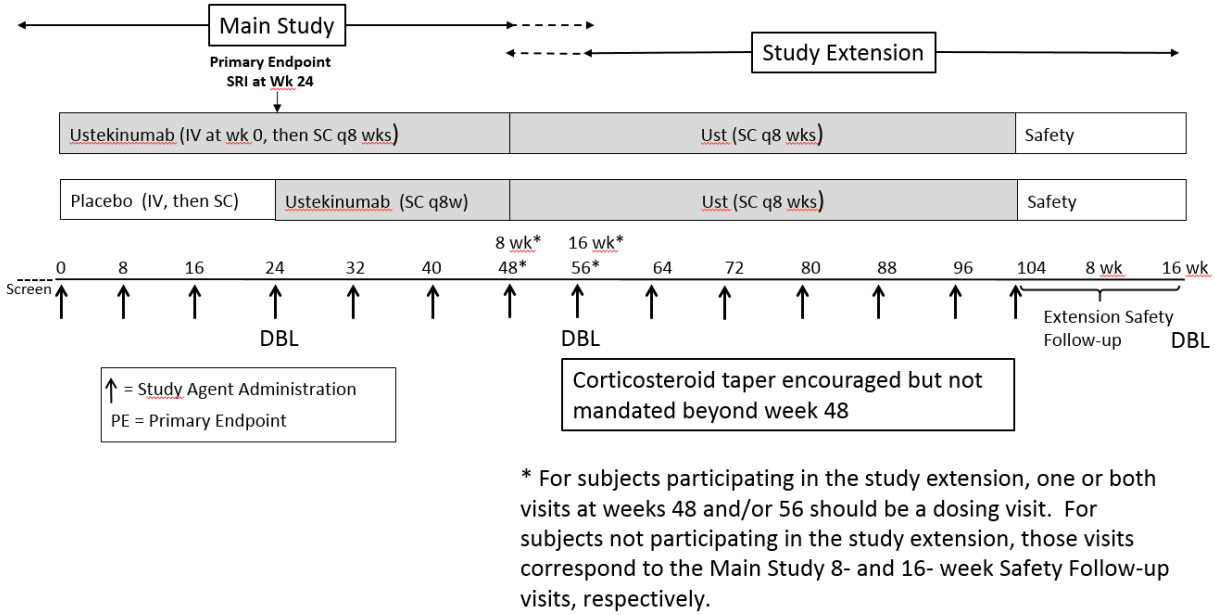
A diagram of the main study design is provided below in Figure 1, and a diagram of the extended study is provided in Figure 2.

Figure 1: Schematic Overview of the Main Study (Screening through 16-Week Safety Follow-Up)



Abbreviations: DBL=database lock; FU=follow-up; IV=intravenous; PE=primary endpoint; PL=placebo; q8w=every 8 weeks; SC=subcutaneous; SLE=systemic lupus erythematosus; SRI=SLEDAI-2K Responder Index; Wks=weeks.

Figure 2: Schematic Overview Including the Study Extension



* For subjects participating in the study extension, one or both visits at weeks 48 and/or 56 should be a dosing visit. For subjects not participating in the study extension, those visits correspond to the Main Study 8- and 16- week Safety Follow-up visits, respectively.

3.2. Study Design Rationale

Blinding, Control, Study Phase/Periods, Treatment Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment. Randomization 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 characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

DNA and Biomarker Collection

It is recognized that genetic variation can be an important contributory factor to interindividual differences in drug distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to a drug. The goal of the pharmacogenomic component is to collect deoxyribonucleic acid (DNA) to allow the identification of genetic factors that may influence the pharmacokinetics, pharmacodynamics, efficacy, safety, or tolerability of ustekinumab and to identify genetic factors associated with SLE.

Biomarker samples will be collected to evaluate the mechanism of action of ustekinumab or help to explain inter-individual variability in clinical outcomes or may help to identify population subgroups that respond differently to a drug. The goal of the biomarker analyses is to evaluate

the pharmacodynamics of ustekinumab and aid in evaluating the drug-clinical response relationship.

DNA and Biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

4. SUBJECT POPULATION

The target study population is subjects with SLE according to SLICC criteria and SLEDAI-2K score ≥6, despite conventional treatment (eg, immunomodulators, antimalarial drugs, corticosteroids, NSAIDs, anti-hypertensive drugs, and/or topical medications). Subjects must have at least 1 BILAG A and/or 2 BILAG B domain scores observed during screening. In addition, subjects must have at least 1 positive autoantibody test (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, and they must also have a clinical SLEDAI-2K score ≥4 (excluding laboratory results) prior to randomization at week 0.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria, the investigator should consult with the appropriate Sponsor representative before enrolling a subject in the study.

Subjects with SLE enrolling into the main study with active cutaneous lupus (including subjects with discoid lupus erythematosus, subacute cutaneous lupus erythematosus, or SLE malar rash or other SLE skin lesions characterized by erythema and/or scale) will be evaluated using CLASI scoring. In addition, subjects who provide consent will be enrolled in the cutaneous lupus substudy evaluating the histology of cutaneous biopsies and/or skin photographs. Biopsy samples (2 samples, 4 mm size) from consenting subjects will be collected prior to dosing at Week 0 and at Week 24 from a lesion demonstrating active cutaneous disease. Subjects participating in the cutaneous lupus substudy are not required to undergo biopsies, and may allow only photographs to document changes in an identified cutaneous lesion or area of active disease. Subjects with cutaneous lupus deemed unsuitable for biopsy (eg, malar rash or alopecia) can also be enrolled in the substudy, and may be evaluated by photography.

If a subject has failed screening and investigator wishes to rescreen the subject, this should be discussed with the study Sponsor and/or their designee. Only 1 rescreening is allowed per subject (also see Section 9.1.2).

The study extension population will be comprised of those subjects who have not permanently discontinued study treatment before or at the Week 40 dose and for whom the investigators judge that there is a potential benefit that outweighs the potential risks to continued ustekinumab treatment.

For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination.

4.1. Inclusion Criteria

4.1.1. Inclusion Criteria Applicable to All Subjects

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

1. Subject must be between 18 (or older as per local requirements) and 75 years of age, inclusive, and weigh at least 35 kg.

2. Subjects must have documented medical history to meet SLICC classification criteria for SLE for a minimum of 3 months prior to first dose (Table 3).

   Subjects eligible for enrollment in this study must qualify as having SLE by meeting the SLICC classification criteria for SLE[25] based upon 1 or both of the following:

   - Meeting 4 criteria with at least 1 clinical criterion and at least 1 immunologic criterion, or
   - A diagnosis of lupus nephritis with presence of at least 1 of the immunological variables

Table 3: Clinical and Immunological Criteria Used in the SLICC Classification Criteria*[25]

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*

Table 3: Clinical and Immunological Criteria Used in the SLICC Classification Criteria*[25]	
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
	  ○ Or pleural effusions
	  ○ Or pleural rub
	• Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day
	  ○ Or pericardial effusion
	  ○ Or pericardial rub
	  ○ Or pericarditis by EKG
	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
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/mm3 at least once)	*In the absence of other known causes such as corticosteroids, 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

Table 3: Clinical and Immunological Criteria Used in the SLICC Classification Criteria*[25]	
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	

3. To be eligible for study enrollment, subjects must have:

   - At least 1 well-documented (subject file, referring physician letter, or laboratory result) unequivocally positive, documented test for autoantibodies in medical history including either of the following: ANA, and/or anti-dsDNA antibodies, and/or anti-Smith antibodies (Section 9.1.2).

   - At least 1 unequivocally positive autoantibody test including ANA and/or anti-dsDNA antibodies and/or anti-Smith antibodies (Section 9.1.2) detected during screening.

   - At least 1 BILAG A and/or 2 BILAG B domain scores observed during screening prior to first administration of study agent.

4. Demonstrate active disease based on SLEDAI-2K score ≥6 observed during screening and assessed approximately 2 to 6 weeks prior to randomization. Must also have SLEDAI-2K ≥4 for clinical features (ie, SLEDAI excluding laboratory results) at Week 0 prior to the first administration of study agent.

5. Data from the SLICC, SLEDAI and BILAG evaluations will be reviewed and adjudicated by the Sponsor and/or the Sponsor-selected independent reviewer(s). For subjects to receive their first administration of study agent, approval must be received by the Sponsor and/or Sponsor-selected independent reviewers.

6. If using oral corticosteroids, subjects must be receiving this medication for at least 6 weeks and on a stable dose equivalent to an average dose of ≤20 mg/day of prednisone for at least 4 weeks prior to the first administration of study agent. If currently not using corticosteroids, must have not received oral corticosteroids for at least 6 weeks prior to the first administration of study agent.

7. If using antimalarials (eg, chloroquine, hydroxychloroquine, or quinacrine), subjects must have used the medication for ≥8 weeks and be on a stable dose for at least 6 weeks prior to the first administration of study agent.

8. If using immunomodulatory drugs (mycophenolate mofetil [MMF]/mycophenolic acid [MPA] ≤2 g/day, azathioprine/6 mercaptopurine (AZA /6 MP) ≤2 mg/kg/day and/or MTX ≤25 mg/wk with concomitant folic acid [recommend ≥5 mg/wk]), subjects must be receiving a stable dose for at least 6 weeks prior to the first administration of study agent.

9. If receiving regular treatment with NSAIDs or other analgesics, subjects must be receiving stable dosing for at least 2 weeks prior to first administration of study agent.

10. Before randomization, a woman must be either:

    Not of childbearing potential: premenarchal; postmenopausal (>45 years of age with amenorrhea for at least 12 months); permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy); or otherwise be incapable of pregnancy.

    Of childbearing potential and practicing a highly effective method of birth control consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: eg, established use of oral, injected or implanted hormonal methods of contraception associated with inhibition of ovulation; placement of an intrauterine device or intrauterine system; male partner sterilization (the vasectomized partner should be the sole partner for that subject); true abstinence (when this is in line with the preferred and usual lifestyle of the subject).

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

11. A woman of childbearing potential must have a negative serum pregnancy test β-human chorionic gonadotropin [β-hCG]) at screening, and a negative urine pregnancy test at Week 0 before the first administration of study agent.

12. Women of childbearing potential must be willing to remain on a highly effective method of birth control during the study and for 4 months after receiving the last study agent. Also, women of childbearing potential must agree to not 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.

13. 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, and all men must also not donate sperm during the study and for 4 months after receiving the last dose of study agent.

14. Are considered eligible according to the following tuberculosis (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, have a negative QuantiFERON®-TB Gold test result (Attachment 2), or have a newly identified positive QuantiFERON®-TB Gold 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 3), 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 Gold test is not approved/registered in that country or the tuberculin skin test is mandated by local health authorities.

        i. Subjects with persistently indeterminate QuantiFERON®-TB Gold test results 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 Gold 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. Subjects who test positive for TB by a TB test other than QuantiFERON®-TB Gold and TB skin test and who have no evidence of TB on chest radiograph will in the context of this protocol be considered latent TB positive and be required to undergo evaluation by a TB specialist and receive treatment for TB to be eligible for this study.

f. Have a chest radiograph (both posterior-anterior and lateral views) 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.

15. Have laboratory test results within the following parameters at screening:

Hemoglobin	≥8.5 g/dL	(SI: ≥85 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)
White blood cells	≥2.0 x 10^3/μL	(SI: ≥2.0 GI/L)

The aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels must be within 2 x upper limit of normal (ULN) range for the laboratory conducting the test. For subjects within the range of 1.5 to 2 x ULN for transaminases, the subject may be included only if the investigator judges the abnormalities or deviations from normal to not be clinically significant or to be appropriate and reasonable for the population under study. 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.

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 promptly reported to the Sponsor's medical monitor and recorded in the subject's source documents and initialed by the investigator.

16. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

17. Each subject must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study.

18. Each subject must sign a separate informed consent form if he or she agrees to provide an optional DNA sample for research (where local regulations permit). Refusal to give consent for the optional DNA research sample does not exclude a subject from participation in the study.

4.1.2. Additional Inclusion Criteria for the Cutaneous Lupus Substudy

To be enrolled in the cutaneous lupus substudy, an SLE subject must satisfy all previously listed inclusion criteria (Section 4.1.1) in addition to the criteria listed below:

1. Have diagnosis of active CLE at screening as well as documented cutaneous disease prior to study enrollment, including subjects with discoid lupus erythematosus, subacute cutaneous lupus erythematosus, or SLE malar rash or other SLE skin lesions including those characterized by erythema and/or scale.

2. Subjects taking systemic, topical, or intra-lesional medications for CLE must be on a stable dose or treatment regimen for 4 weeks prior to first study agent administration.

3. Subjects who consent to participate in the cutaneous lupus substudy will be asked to provide biopsies of an active CLE target lesion prior to dosing at Weeks 0 and 24. An active CLE lesion is characterized by scale and/or erythema, excluding previously scarred tissue. In addition, separate consent will be obtained to collect photographs of a cutaneous lesion or area of active disease according to the schedule defined in Table 1.

4. Subjects with cutaneous lupus deemed unsuitable for biopsy (eg, malar rash or alopecia) can also be enrolled in the substudy, and may be evaluated by photography.

4.1.3. Inclusion Criteria Applicable to All Subjects Entering into the Study Extension (Week 48 or Week 56 visits)

Any subjects who do not meet the inclusion criteria for the study extension must follow the Time and Events schedule for the main study design (Table 1), and have safety follow-up visits conducted at 8 and 16 weeks following their Week 40 or final study dose.

1. Subjects must not have permanently discontinued study treatment on or before their Week 40 visit, and are able to either continue q8w SC dosing at approximately 8 weeks (±2 weeks) after their Week 40 visit, or are able to resume dosing at Week 56 with no more than 16 weeks (±2 weeks) since their Week 40 visit.

2. In the judgment of the study investigator, the potential benefit of continuing ustekinumab long-term treatment outweighs the potential risks for the subject.

3. Each subject must sign a revised informed consent indicating agreement to participate in the extended study.

4.2. Exclusion Criteria

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

1. Have other inflammatory diseases that might confound the evaluations of efficacy, including but not limited to rheumatoid arthritis (RA), psoriatic arthritis (PsA), RA/lupus overlap, psoriasis, or active Lyme disease.

2. Are pregnant, nursing, or planning a pregnancy or fathering a child while enrolled in the study or within 4 months after receiving the last administration of study agent.

3. Have received systemic or topical cream/ointment preparations of cyclosporine A or other systemic immunomodulatory agents other than those described in inclusion criteria within the past 3 months prior to first administration of study agent (Section 4.1). Corticosteroids are not included in this criterion; see Sections 4.3 and 8.3 regarding corticosteroids.

4. Have received a single B cell targeting agent within 3 months prior to first study agent administration; or received more than 1 previous B cell targeting therapy including belimumab or epratuzamab within 6 months prior to first administration of the study agent; or received B cell depleting therapy (eg, rituximab) within 12 months prior to first administration of the study agent or have evidence of continued B cell depletion following such therapy.

5. Have ever received ustekinumab.

6. Have received prior immunomodulatory biologic therapy for lupus not described in Exclusion Criterion #4 including, but not limited to, tocilizumab, alefacept, efalizumab, natalizumab, abatacept, anakinra, brodalumab, secukinumab, ixekizumab, or inhibitors of TNF, IL-1, IL-6, IL-17, or interferon pathways, less than 5 half-lives or 3 months, whichever is longer, prior to first administration of the study agent.

7. Have a known hypersensitivity to human immunoglobulin (Ig) proteins (eg, intravenous Ig).

8. Have used oral cyclophosphamide within 90 days or IV cyclophosphamide within 180 days of starting screening.

9. Have a history of active granulomatous infection, including histoplasmosis, or coccidioidomycosis, prior to screening. Refer to inclusion criteria for information regarding eligibility with a history of latent TB.

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

11. Have 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.

12. Have had a nontuberculous mycobacterial infection or opportunistic infection (eg, cytomegalovirus, pneumocystosis, aspergillosis) within 6 months prior to screening.

13. Have received, or are expected to receive, any live virus or bacterial vaccination within 3 months before the first administration of study agent, during the study, or within 3 months after the last administration of study agent. For BCG vaccination criterion, see Exclusion Criterion 10 and Prohibition/Restriction Criterion 8.

14. Have had a serious infection (including but not limited to, hepatitis, pneumonia, sepsis, or pyelonephritis), or have been hospitalized for an infection, or have been treated with intravenous antibiotics for an infection within 2 months prior to first administration of study agent. Less serious infections (eg, acute upper respiratory tract infection, simple urinary tract infection) need not be considered exclusionary at the discretion of the investigator.

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

16. Subject has a history of human immunodeficiency virus (HIV) antibody positive, or tests positive for HIV at screening.

17. 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).

18. Subjects who are seropositive for antibodies to hepatitis C virus (HCV), unless they have 2 negative HCV RNA test results 6 months apart prior to screening and have a third negative HCV RNA test result at screening.

19. Subjects having experienced a recent single dermatomal herpes zoster eruption within the past 4 months are excluded. Those with multi-dermatomal herpes zoster or central nervous system (CNS) zoster within the past 5 years are excluded.

20. Subjects with a history or suspected occurrence of drug-induced lupus.

21. Have urinary protein >4 g/day or protein/creatinine ratio >4.

22. Have inherited complement deficiency or combined variable immunodeficiency.

23. Have end-stage renal disease, or severe or rapidly progressive glomerulonephritis, including severe, active lupus nephritis reported in recent biopsy and/or other assessments such as active urinary sediment, rapidly increasing creatinine, or other factors that suggest severe or rapidly progressing nephritis (see also limits on serum creatinine in Inclusion Criterion #15).

24. Have severe CNS lupus including but not limited to seizures, psychosis, transverse myelitis, CNS vasculitis and optic neuritis.

25. Have severe, progressive, or uncontrolled hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurologic/ cerebral, or psychiatric disease, or current signs and symptoms thereof.

26. Have 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.

27. Subject has a 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 surgically cured).

28. Has known allergies, hypersensitivity, or intolerance to ustekinumab, its excipients or latex (contained in the syringe needle cover, see Section 14.1) (refer to the ustekinumab Investigator's Brochure).

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

30. Has received an investigational drug that is not previously defined in other exclusion criteria (including investigational vaccines or other medications specified in section 4.3, Prohibition/Restriction No. 3) 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 drug, or is currently enrolled in an interventional study.

31. Has any condition for which, in the opinion of the investigator and/or Sponsor, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments including a previous pattern of non-compliance with medical follow-up or being deemed unlikely to be compliant with a study visit schedule.

32. 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 drug administration.

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

33. Have a transplanted organ (with the exception of a corneal transplant performed >3 months prior to first administration of study agent).

34. Have or have had a substance abuse (drug or alcohol) problem within the previous 3 years.

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

36. Subject is an employee of the investigator or study site (i.e. 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.

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

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of study drug 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, Source Documentation, describes the required documentation to support meeting

the enrollment criteria. Sponsor reserves the right to discontinue the subject for any operational or safety reasons.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study (including the study extension) to be eligible for continued dosing in the study:

1. If a woman is capable of pregnancy, she must remain on a highly effective method of birth control during the study and for 4 months after receiving the last study agent. The exception to this restriction is if the subject or her male partner is sterilized; this situation does not require birth control. A woman must not 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.
2. If a man, he is to use an effective method of birth control and not donate sperm during the study and for 4 months after receiving the last dose of study agent. The exception to this is if the subject or his female partner is sterilized; this situation does not require birth control.
3. Use of additional immunosuppressants or immunomodulators, other than those explicitly allowed in the inclusion/exclusion criteria, are prohibited including but not limited to the following:

    - Biologic agents targeted at reducing TNFα (including but not limited to infliximab, golimumab, certolizumab pegol, etanercept, yisaipu, CT-P13 [Remsima®] and adalimumab)
    - B cell depleting 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])
    - Interleukin-1 inhibitors (eg, canakinumab)
    - Interferon inhibitors
    - IL-1ra (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)
    - Tacrolimus or picrolimus, oral or topical preparations
    - Toll-like receptor inhibitors

- Thalidomide or lenalidomide
- Dapsone
- Adrenocorticotropic hormone (ACTH) by injection

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

5. Multiple administrations of high doses of corticosteroids, and initiation of medium or high potency topical corticosteroids, are prohibited during the study as defined in Section 8.3.

6. The initiation of a new permitted immunomodulatory agent (MTX, azathioprine, 6-mercaptopurine, mycophenolate mofetil/mycophenolic acid) in addition to an ongoing immunomodulatory therapy is prohibited.

7. Initiation of new angiotensin II receptor blocker (ARB) or angiotensin-converting enzyme (ACE) inhibitor therapy after first dose of study agent is not permitted for the treatment of lupus-related disease through Week 28.

8. 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 3 months after receiving the last administration of study agent.

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

10. The use of complementary therapies that may trigger activation of lupus or mitigate the symptoms of SLE, including but not limited to, traditional medicine (eg, herbal/alternative preparations [eg, Echinacea], Chinese, acupuncture, ayurvedic) is prohibited through Week 40.

11. Study subjects should avoid excessive sun exposure and may not participate in commercial ultraviolet tanning or ultraviolet phototherapy during the study.

12. Skin concealers or topical tan preparations should be avoided due to their potential to obscure skin disease activity.

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

5. TREATMENT ALLOCATION AND BLINDING

5.1. Procedures for Randomization

Dynamic central randomization will be implemented in conducting this study. Subjects will be assigned to 1 of 2 treatment groups based on a minimization randomization algorithm

implemented in the interactive web response system (IWRS) before the study. Dynamic central randomization targets to balance the distribution of subjects to achieve the randomization ratio (3:2) at the study level and within the levels of each individual stratification factor: skin biopsy (y/n, when n<16 for y), presence of lupus nephritis (y/n), baseline SLE medications and SLEDAI-2K score (combined factor)*, site, region (approximately 4 categories), and race (3 categories). Based on the algorithm, each subject will be assigned to the treatment group which will produce minimum total imbalance score with a high probability, where the total imbalance score is a weighted average of the imbalance scores for each stratification factor and for the whole study. The IWRS will the assign a unique treatment code, which will dictate the treatment assignment for the subject.

* The baseline SLE medications and SLEDAI-2K score will be calculated as a combined factor, including:

- SLEDAI-2K score (<10 or ≥10) combined with
- Baseline medications:
  - High medications defined as ≥15 mg/wk MTX, or ≥1.5 mg/kg/day AZA/6-MP, or ≥1.5 g/day MMF/MPA, and/or ≥15 mg/day prednisone.
  - Low medications defined as <15 mg/wk MTX, or <1.5 mg/kg/day AZA/6-MP, or <1.5 g/day MMF/MPA, and/or <15 mg/day prednisone.

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.

Under normal circumstances, the blind should not be broken until all subjects have completed the study at Week 56 or terminated study participation, and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by contacting IWRS. It is recommended that the investigator contact the Sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the Sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the Sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented by the IWRS, in the appropriate section of the case report form (CRF), and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

Subjects who have had their treatment assignment unblinded may be discontinued from further administration of study agent and should return for safety follow-up.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. The Sponsor will be blinded through the Week 24 evaluation and until the database is cleaned and finalized for planned analyses. The clinical site, subjects, investigators, and site personnel will remain blinded through the end of the study until Week 56 data are finalized. Data that may potentially unblind the treatment assignment will be handled with special care.

6. DOSAGE AND ADMINISTRATION

Detailed instructions on the IV and SC administration of study agent are provided in the Investigative Product (IP) Manual.

6.1. IV administration

For IV administration, the study agent will be administered to each subject over a period of not less than 1 hour.

Ustekinumab 5 mg/mL Final Vialed Product (FVP) (IV) is supplied as 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 for FVP (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, 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 patients 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 adjusted 6 mg/kg dosing. Comparable numbers of vials will be administered to subjects receiving placebo based on their body weight-range. The body weight-range doses are based on the following:

- Body weight ≥35 kg and ≤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)

6.2. SC administration

Ustekinumab will also be supplied as a single-use latex-free 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.

Week 0 up to Week 24 (Blinded Study Agent Administration Phase)

Group 1: Subjects will receive weight-range based IV dosing of approximately 6 mg/kg of ustekinumab at Week 0 followed by ustekinumab 90 mg SC administrations at Weeks 8 and 16.

Group 2: Subjects will receive weight-range based IV dosing of placebo at Week 0 followed by placebo SC administrations at Weeks 8 and 16.

Week 24 to Week 40 (Cross-over Administration Phase)

Group 1: Subjects will receive an ustekinumab 90 mg SC administration at Week 24 followed by q8w administrations through Week 40.

Group 2: Subjects will cross-over to ustekinumab 90 mg SC administrations at Week 24 followed by q8w administrations through Week 40.

After Week 40 to 16-Week safety Follow-up (Safety Follow-up Phase)

Groups 1 and 2: Subjects who do not participate in the study extension are expected to return for safety follow-up visits at Weeks 44 and for 8- and 16-weeks safety follow-up.

Study Extension (Week 48/Week 56 through Week 120)

Subjects who meet the study extension inclusion criteria will receive open-label ustekinumab administration for the purpose of expanding the safety experience and maintenance of efficacy in lupus patients continuously exposed to ustekinumab 90 mg q8w. Subjects who continue dosing in the extended study starting at Week 48 or at Week 56 will receive open-label ustekinumab SC dosing through Week 104. If the development of ustekinumab in SLE is terminated, then the study extension will also be discontinued.

7. TREATMENT COMPLIANCE

Study personnel will maintain a log of all study agent administrations. Study agent supplies for each subject will be inventoried and accounted for. All ongoing therapies administered at the time of screening must be recorded.

Compliance with the treatment schedule is strongly encouraged. It is understood that treatment may be interrupted for health-related or safety reasons. The Weeks 0, 24, and 48 visits are essential for assessing efficacy and safety of ustekinumab as therapy for active SLE.

Therefore, if for any reason a subject cannot receive a dose of study agent at the scheduled visits, the subjects must make every effort to come for scheduled assessments. Through the Week 32 visit, the visit and study agent administration should occur within ± 7 days of the scheduled visit day (relative to Week 0). Following the Week 32 visit, the study agent administrations are allowed to occur within ±2 weeks of the scheduled visit day (relative to Week 0). The study agent administrations are scheduled to occur approximately 8 weeks apart, and cannot occur <14 days apart. If there is a delay in treatment, the subject should resume the normal study schedule relative to the baseline visit (Week 0).

All subject's electronic case report forms (eCRFs) will be monitored by a site monitor designated by the Sponsor. During these monitoring visits, all procedures will be evaluated for compliance with the protocol. Subject charts will be reviewed and compared with the data entries on the eCRFs to ensure accuracy. The Sponsor must be contacted for any deviation to the timeframes above.

8. CONCOMITANT THERAPY

All prestudy therapies administered up to 90 days before entry into screening must be recorded at screening. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study. All concomitant therapies must be recorded throughout the study beginning at entry into screening and any changes must be recorded throughout the study.

Every reasonable effort should be made to keep concomitant medications stable at least through Week 28, and if possible also through the main study 8-week safety follow-up or through the study extension (if applicable). With the exception of corticosteroids (see Section 8.3 regarding corticosteroid tapering), all other concomitant medications should be maintained at stable doses throughout the study. A concomitant medication may be reduced or medication temporarily discontinued because of abnormal laboratory values, side effects, 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. If concomitant medications have been adjusted after randomization as allowed per protocol, every effort should be made to return subject back to the baseline (Week 0) dose level by the Week 12 visit; or increased medication use (relative to baseline) may render a subject to be considered a treatment failure. Corticosteroid adjustments for cause are permitted as defined in Section 8.3.

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

All pharmacologic therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements) different from the study agent must be recorded in the

concomitant therapy section of the eCRF. Subject diary cards will be used to capture changes in subject-administered medications that occur in between study visits during the main portion of this study, and these changes must also be recorded in the concomitant therapy section of the eCRF.

8.1. Immunomodulators

If receiving immunomodulators, subjects should be receiving stable dosing from screening through Week 28. Subjects can be receiving MMF/MPA (≤2 g/day), azathioprine/6-mercaptopurine (≤2 mg/kg/day) and/or MTX (≤25 mg/wk) with concomitant folic acid (recommend ≥5 mg/wk), during screening and through Week 28. A reduction in immunomodulators from Week 12 through Week 28 is allowed only if the subject develops unacceptable side effects, with the implication that this may affect interpretation of the subjects' 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 between the Week 12 and 24 visit will cause subjects to be considered a treatment failure for the purposes of the primary endpoint analysis. Permanent discontinuation of the study treatment must be considered for subjects receiving an increase (relative to baseline) in their immunomodulator dose. Beyond Week 28, immunomodulators should remain as stable as possible through the 8-week safety follow-up or through the study extension (if applicable); however, dose adjustment is allowed for unacceptable side effects.

8.2. Antimalarial Medications

Stable treatment with hydroxychloroquine, chloroquine, or quinacrine is permitted through the 8-week safety follow-up. Beyond Week 28, it is permitted to introduce or adjust dosing of antimalarials. Antimalarials produced by a licensed compounding pharmacy (eg, quinacrine) in the country of administration and using pharmacaceutical grade components are allowed.

8.3. Corticosteroid Therapy

Unnecessary dose changes are discouraged, and any dose adjustments should be made in increments. Changes in corticosteroids through the 8-week safety follow-up or through the study extension (if applicable) are allowed for medical necessity, but the degree and timing of the adjustment should be carefully considered as this may have an impact on the study results, especially during the period between 12 and 28 weeks.

Oral Corticosteroids*

If using oral corticosteroids, must be receiving this medication for at least 6 weeks and on a stable dose equivalent to an average dose of ≤20 mg of prednisone/day for at least 4 weeks prior to the first administration of study agent. Corticosteroid dose adjustment (increase or decrease) of no more than 5 mg prednisone (equivalent/day) to a maximum dose of 25 mg/day is permitted through Week 6. From Week 6 through Week 12, no corticosteroid dose increases are permitted, and within this window only a gradual decrease of up to 5.0 mg prednisone (equivalent/day) adjustment towards the baseline dose are allowed up to the Week 12 visit. No further adjustments in doses of corticosteroid for the treatment of SLE disease are permitted between

Weeks 12 and 28. Following Week 28, changes in corticosteroid dosing through the 8-week safety follow up is allowed for medical necessity, but the degree and timing of the adjustment should be carefully considered as this may have an impact on the study. Dose increases of oral corticosteroids of 40 mg/day or more should be discussed with the medical monitor and may result in discontinuation of study agent administration.

Subjects may receive short courses (2 weeks or less) of oral corticosteroids for reasons such as prophylactic therapy before surgery (stress-dose corticosteroids) or therapy for limited infections, exacerbation of asthma, or chronic obstructive pulmonary disease.

Subjects likely to require multiple courses of steroids for reasons other than SLE should be excluded from study participation.

Gradual tapering of oral corticosteroid dosing in the study extension (recommended reductions of no more than 10 to 20% of the original dose per week) is encouraged starting after the Week 48 dose at the discretion of the study investigator. Tapering to the lowest possible maintenance dose of corticosteroids is recommended, including complete weaning off of corticosteroids if possible. It is recommended that subjects should be educated and monitored by study staff for symptoms of steroid deficiency (eg, Addisonian symptoms) during periods of steroid tapering, as appropriate.

If subjects experience a worsening in their disease activity while tapering corticosteroids, further dose decreases may be suspended, and/or their oral corticosteroid dose may be temporarily increased if deemed necessary by the investigator. For subjects whose corticosteroid taper is interrupted, investigators are encouraged to resume tapering within 4 weeks.

In the event of increased corticosteroid dosing, it is recommended that the average dose should not be increased above the baseline dose unless medically necessary. Discretion should be used as any corticosteroid increases may render a subject to be considered a treatment or steroid tapering failure. Sustained oral corticosteroid doses of 40 mg/day or higher may result in discontinuation of study agent.

*Rectal administration of corticosteroids, if necessary, should be short-term and using topical preparations.

Epidural, Intravenous, Intramuscular, Intra-articular, and Intra-lesional Corticosteroids

Epidural, IV, IM, IA, or intra-lesional administration of corticosteroids is strongly discouraged within 4 weeks prior to the first administration of study agent and is not allowed for the treatment of SLE through Week 28. Drugs that induce release of endogenous steroids such as ACTH administered by injection are not allowed within 3 months prior to the first administration of study agent and throughout the study. Short-term (≤2 weeks) epidural, IV, IM, IA, or intra-lesional corticosteroid use for the treatment of indications other than SLE should be limited to situations where, in the opinion of the treating physician, there are no adequate alternatives. If clinically necessary, a total of 1 or 2 IA injections may be permitted up to the Week 16 dosing,

however this would render those joints unevaluable for subsequent assessments. For conditions other than SLE, corticosteroid therapy should be limited to situations in which, in the opinion of the treating physician, there are no adequate alternatives. Intravenous corticosteroids of >625 mg prednisone equivalent/day for 2 or more days total in the 24-week period will be evaluated for treatment failure as per the statistical analysis plan (SAP).

Inhalation Corticosteroids

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

Corticosteroid Use in Cutaneous Lupus Substudy

For subjects in the cutaneous lupus substudy, the initiation of, or an increase from baseline in, the use of potent topical corticosteroids, or intra-lesional corticosteroid injections, is not allowed and should be avoided through the 8-week safety follow-up or in the study extension.

8.4. Nonsteroidal Anti-inflammatory Drugs

Subjects treated with NSAIDs, including aspirin and selective cyclooxygenase-2 (COX-2) inhibitors, and other analgesics should receive the usual marketed doses approved in the country in which the study is being conducted. 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 drug and through Week 28, and may be changed only if the subject develops unacceptable side effects. After Week 16 and through Week 28 the addition of new NSAIDs to the treatment regimen is not permitted. Minor adjustments in NSAID therapy are allowed after Week 28 although it is recommended that the use of any NSAIDS remain as stable as possible, and any notable changes should be recorded.

8.5. Anti-hypertensive Medications

Subjects are permitted to receive stable doses of ARB or ACE inhibitors for the treatment of hypertension and lupus. Initiation of new ARB or ACE inhibitor therapy after first dose of study agent is not permitted for the treatment of lupus-related disease through Week 28. Subjects should not initiate any new ARB or ACE inhibitor therapy between randomization and Week 28. New or adjusted ARB or ACE inhibitor therapy is allowed beyond Week 28.

8.6. Topical Medications

Topical medications are permitted; however, topical compounds cannot include a prohibited medication. Topical ointments or creams of cyclosporine A are prohibited through Week 28; however ophthalmic use is permitted. Low potency topical steroids are allowed except on day of study visit. Medium to high potency topical corticosteroids are disallowed for all subjects through the 8-week safety follow-up, and high potency topical corticosteroids are not allowed during the study extension. For subjects in the cutaneous lupus substudy, topical treatment of target lesions should remain stable during the cutaneous lupus substudy period. For 72 hours prior to study visit, topical medications should not be applied to lesions under evaluation.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the frequency and timing of efficacy, pharmacokinetics, antibodies to ustekinumab, pharmacodynamics, pharmacogenomics, health-related quality of life, safety, and other measurements applicable to this study.

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.

The total blood volume to be collected from each subject over the course of the main portion of the study will be approximately 640 mL. The total blood volume to be collected in the study extension between Weeks 48 and 120 will be approximately 250 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the collection or analysis of specific samples.

A blood sample will be collected from subjects who have consented to participate in the pharmacogenomics component of the study. In the event of DNA extraction failure, a replacement pharmacogenomics blood sample may be requested from the subject. A separate informed consent would not be required to obtain a replacement sample.

Subjects who have consented to participate in the cutaneous lupus substudy will be requested to allow collection of skin biopsy samples at Week 0 and at Week 24. In addition, photographs will be taken of a target cutaneous lesion or area of active disease as noted in the Time and Events Schedule (Table 1). For additional detail regarding the cutaneous lupus substudy, refer to Section 9.7.

9.1.2. Screening Phase

9.1.2.1. Screening Procedures

Written informed consent must be obtained and reviewed by investigator before any screening data is collected.

Screening procedures will be performed as indicated in the Time and Events Schedule (Table 1). The screening visit must be performed no more than 6 weeks prior to the randomization visit (Week 0). In addition, to be eligible for study participation, subjects must have SLEDAI score ≥ 4 for clinical features at Week 0 and have received approval for study randomization following review and adjudication of screening lupus assessments by the Sponsor and/or Sponsor-selected independent reviewer(s).

Subjects will be trained on how to complete the Diary cards. Diary cards will be distributed to subjects for completion during the screening period.

Women of childbearing potential must have a negative serum β-hCG pregnancy test at screening and a negative urine β-hCG pregnancy test before randomization. Women of childbearing potential and men must consent to use highly effective methods of contraception (see inclusion criteria, Section 4.1) and continue to use contraception for the duration of the study and for 4 months after the last study agent administration. The method(s) of contraception used by each subject must be documented.

All screening evaluations establishing subject eligibility will be performed and reviewed by investigator before subject can be randomized. Although the SLICC criteria may not have been formally assessed, to be eligible for enrollment subjects must have demonstrated symptoms (documented in subject file) of SLE sufficient to meet SLICC criteria for a minimum of 3 months prior to first dose of study agent. Subjects eligible for enrollment in this study must qualify as having SLE by meeting the SLICC classification criteria for SLE based upon 1 or both of the following (as described in Inclusion Criterion #2):

- Meeting 4 criteria with at least 1 clinical criterion and at least 1 immunologic criterion, or
- A diagnosis of lupus nephritis with presence of at least 1 of the immunological variables,

Subjects must also have 1 well-documented (subject file, referring physician letter, or laboratory result) medical historical value for unequivocally positive ANA, anti-dsDNA antibodies, and/or anti-Smith antibodies. Medical historical documentation of a positive test of ANA (eg, ANA by HEp-2 titer, ANA by enzyme-linked immunosorbent assay) or anti-dsDNA (eg, anti-dsDNA by Farr assay or ELISA) must include the date and type of the test, the testing laboratory name, numerical reference range, and a key that explains that the values provided are positive versus negative/equivocal or borderline. Only unequivocally positive values as defined in the laboratory's reference range are acceptable; borderline values will not be accepted.

In addition, in order to assess the stability of SLE disease activity, subjects must demonstrate SLEDAI-2K score ≥6, despite conventional treatment (eg, immunomodulators, antimalarial drugs, corticosteroids, NSAIDs, anti-hypertensive drugs, and/or topical medications). In addition, subjects must have at least 1 positive autoantibody test (ANA, anti-dsDNA antibodies, and/or anti-Smith antibodies) observed during screening. Subjects must also demonstrate at least 1 BILAG A and/or 2 BILAG B domain scores observed prior to first administration of study agent.

9.1.2.2. Retesting

If a subject has signed the ICF and failed to meet at least 1 entry requirement, a one-time retest of screening laboratory test(s) will be allowed in the event of suspected error in sample collection or analysis performance, or a study entry procedure may be repeated once during the screening period if needed. A request to use a local test to replace the central lab test should be discussed with the medical monitor prior to retesting. This is inclusive of only 1 additional blood draw to be completed for retesting, regardless of whether an additional laboratory value is found

to be out of range. The goal of the retest procedure is to assess if the subject is eligible for randomization within the screening window or should be screen failed. Subjects that 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 a screen failure. Exceptions to this are positive QuantiFERON®-TB Gold, 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.

9.1.2.3. Rescreening

If a subject has failed screening and investigator wishes to rescreen the subject, this should be discussed 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, and then restart a new screening phase.

9.1.3. Double-Blind Treatment Phase

9.1.3.1. Week 0/Day of Randomization

At Week 0, 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 participating in the cutaneous lupus substudy will have baseline, pre-treatment photographs and/or skin biopsies collected. Subject's diary card which was distributed during screening will be reviewed at Week 0, and a new card will be provided at each study visit to record medication changes during the subsequent 4 weeks through the main portion of the study.

9.1.3.2. Placebo-controlled Treatment Period (Through Week 24)

After randomization and the first administration of study agent by IV infusion, subjects will have blinded study agent administrations SC q8w through the Week 24 visit. Assessments will be performed as indicated in the Time and Events Schedule (Table 1).

9.1.4. Cross-over Treatment (Through Week 40)

At Week 24, subjects in the placebo group will cross-over to receive ustekinumab dosing, and all subjects will continue to receive SC administrations q8w through Week 40. All subjects will continue to remain blinded to study treatment received during the placebo-controlled treatment period as described in Section 9.1.3.2.

9.1.5. Study Extension (Week 48/Week 56 through Week 104)

Subjects who qualify for participation in the study extension through Week 104 will continue ustekinumab 90 mg q8w SC dosing at approximately 8 weeks (±2 weeks) after their Week 40 visit, or resume ustekinumab dosing at Week 56 with no more than 16 weeks (±2 weeks) since their Week 40 visit.

9.1.6. Subjects Withdrawing from Study Participation

Subjects who withdraw from study participation will not be required to return for any follow-up assessments.

9.1.7. Post-treatment Safety Follow-up

Subjects who permanently discontinue study agent at or before Week 40, or permanently discontinue at or before Week 104 if they are participating in the study extension, but do not withdraw from study participation, should be followed for approximately 16 weeks (5 half-lives) after the last study agent administration according to the visit schedule and assessments indicated in the appropriate Time and Events Schedules (Table 1 and Table 2). Follow-up visits should occur approximately 8 weeks and 16 weeks after the last study agent administration. Subjects who permanently discontinue study agent before or at Week 40 will not be eligible to participate in the study extension.

Telephone contact will be made to determine reasons for study discontinuation for up to 16 weeks after the last dose of study drug, unless the subject is lost to follow-up, or has withdrawn consent. If the information on reason 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 CRF.

9.2. Efficacy

All efficacy evaluations should be consistently performed by the study investigator or sub-investigator to achieve comparable measures over time. Independent adjudication by Sponsor or Sponsor-designated independent reviewer(s) will be performed for key lupus assessments (eg, SLEDAI, BILAG, 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. Evaluations

A complete list describing all efficacy evaluations and endpoints, and which evaluations are included in the composite endpoints is provided in Attachment 1.

9.2.1.1. SLEDAI-2K and S2K RI-50

The SLE disease activity index 2000 (SLEDAI-2K / S2K RI-50 [Baseline]) 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. It is weighted according to the feature. At screening (Attachment 5), 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.[33] At baseline (Attachment 6), the features assessed in the SLEDAI-2K are used for comparison to the S2K RI-50 index described below.

The SLEDAI-2K has been adapted and developed into the SLEDAI-2K Responder Index (S2K RI-50 [Follow-up], Attachment 7)[35], a measure that can document partial improvement in the 24 disease features between SLEDAI-2K assessments.[34] 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 S2K 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."[32] The S2K RI-50 score is the sum of the 24 scored items, which ranges from 0 to 105.

9.2.1.2. BILAG

The BILAG[13,17] index scores subjects based on the need for alterations or intensification of therapy (Attachment 8). The assessing physician will evaluate 97 items divided into the following 9 organ/systems domains.

- Constitutional
- Mucocutaneous
- Neuropsychiatric
- Musculoskeletal
- Cardiorespiratory
- Gastrointestinal
- Ophthalmic
- Renal
- Hematological

The assessing physician ought to consider each item as to its presence in the past 4 weeks, and answer 0=not present, 1=improving, 2=same, 3=worse, or 4=new as compared with a specified reference visit. Each organ/system domain is classified as BILAG A, B, C, D, or E based upon organ/system specific items and criteria specific to the domain.

9.2.1.3. CLASI

Cutaneous lupus erythematosus disease activity will be measured by the CLASI. The CLASI is an instrument the assessing physician will use to assess the disease activity and damage caused to the skin for CLE patients with or without systemic involvement. The CLASI consists of 2 scores; the first summarizes the activity of the disease while the second is a measure of the damage done by the disease (Attachment 9). Activity is scored on the basis of 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] Higher activity and damage scores indicate worse disease activity.

9.2.1.4. Physician Global Assessment of Disease Activity

The physician must complete the Physician Global Assessment of Disease Activity[8] independent of subjects' assessment (Attachment 10). The assessments will be recorded on a visual analogue scale (VAS; 0 to 10 cm). The scale for the assessment ranges from "no Lupus activity" (0) to 'extremely active Lupus" (10).

The physician assessor should preferably be the same person at every study visit for a given subject.

9.2.1.5. Patient Global Assessments

The subject must complete the Patient Global Assessment of Disease Activity and Patient's Assessment of Pain independent of the Physician's Global Assessment of Disease Activity.

9.2.1.5.1. Patient Global Assessment of Disease Activity

The Global Assessment of Disease Activity will be recorded on a visual analogue scale (VAS; 0 to 10 cm). The scale for the assessment ranges from "very well" (0) to "very poor" (10) (see Attachment 11).

9.2.1.5.2. Patient Assessment of Pain

The Patient's Assessment of Pain is used to assess the patient reported pain intensity. The patient's will be asked to assess their average pain during the past week on a visual analogue scale (VAS; 0 to 10 cm). The anchors of the instrument include 0 to represent 'no pain' and 10 to represent 'the worst possible pain.'

9.2.1.6. Short-Form-36

The RAND short-form (SF)-36 questionnaire is a self-administered multi-domain scale with 36 items. Eight health domains cover a range of functioning (Attachment 12):

- 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 subscales are scored from 0 to 100. The scoring yields a Physical Component Summary score and a Mental Component Summary score, a total score, and subscale scores. Higher scores represent better outcomes. It is appropriate for persons over the age of 14 and may be completed in 5 to 10 minutes. Translations are available in most languages; the instrument has undergone extensive linguistic and cultural validation. Version 2 acute will be used in the study.

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.[42] A change of 3 points in any of the subscales or 5 points for the component score is associated with clinically meaningful change.[27,41,40] The SF-36 has been used extensively in clinical trials providing evidence of psychometric properties. Reliability estimates for physical and mental component summary scores exceeded 0.90 in early studies[21] and have been further confirmed in later studies. Construct validation was established through comparison to several other generic health surveys.

9.2.1.7. Fatigue Severity Scale

The Fatigue Severity Scale (FSS) is a 9-item questionnaire designed to assess the severity of fatigue and its impact on daily living using 7 response options (1=Completely Disagree, 7=Completely Agree) during a recall period of the past week (Attachment 13). It can be completed within 5 minutes by the subject. Scores above 36 of the total possible score of 63 reflect increasing severity of fatigue. The scale was developed for use in SLE.[19] The scores on the scale correlate with patient reported pain, sleep, depression, and with each subscale of the SF-36. The FSS has shown a high internal consistency, and differentiates patients from controls in studies with SLE subjects. The instrument was translated from the original English version and is available in several languages.

9.2.2. Definitions

A complete list describing all efficacy evaluations and endpoints, and which evaluations are included in the composite endpoints is provided in Attachment 1.

9.2.2.1. SRI-4

Systemic Lupus Erythematosus Disease Activity Index 2000 SRI-4 response is defined as a composite endpoint requiring at least a 4 point reduction in SLEDAI 2K score (Section 9.2.1.1), no worsening (<10 mm increase) from baseline in the Physician's Global Assessment of Disease Activity score (PGA) (Section 9.2.1.4), and no new BILAG Domain A and no more than 1 new BILAG Domain B scores (Section 9.2.1.2).[9] SRI-5 and SRI-6 are similarly defined with response requiring a ≥5 point reduction or ≥6 point reduction in SLEDAI 2K, respectively.SRI-5 and SRI-6 are similarly defined with response requiring a ≥5 point reduction or ≥6 point reduction in SLEDAI-2K, respectively.

9.2.2.2. BILAG-based Combined Lupus Assessment

The BILAG-based Combined Lupus Assessment (BICLA) requires patients to meet response criteria across 3 assessment tools: (1) the BILAG-2004 index (2) the SLEDAI index and (3) a

PGA. Patients are identified as responders or non-responders based upon the following requirements:[39]

Requirements for BICLA Response	
BILAG	BILAG improvement classified as: • All BILAG A scores at baseline improved to either BILAG B,C or D • All BILAG B scores at baseline improved to either BILAG C or D • No worsening in disease activity defined as no new BILAG A scores and ≤1 new BILAG B score
SLEDAI-2K	No worsening of total SLEDAI-2K from baseline (change ≤0)
PGA	No significant deterioration (<10 mm increase) in 100 mm visual analogue PGA
Treatment Failure	No treatment failure (see SAP for definition of treatment failure)

9.2.2.3. Flares

[redacted]

9.2.2.4. S2K RI-50 Response

S2K RI-50 response is defined as a decrease of at least 6 points from baseline in the SLEDAI-2K score.

9.2.2.5. No Worsening in PGA

No worsening in PGA is defined as less than a 10 mm increase on 100 mm VAS.

9.2.3. Endpoints

Primary Endpoint

The primary endpoint of this study is the proportion of subjects with a composite SRI-4 response at Week 24.

Major Secondary Endpoints

The major secondary endpoints are listed in order of importance as specified below:

1. The change from baseline in SLEDAI-2K at Week 24.
2. The change from baseline in PGA at Week 24.
3. The proportion of subjects with BICLA response at Week 24.

Other Endpoints

[redacted]

SLE Disease activity:

6. The proportion of subjects with responses in SRI-4, SRI-5, SRI-6, S2K RI-50 response and BICLA over time.
7. [redacted]

9. The absolute change from baseline in SLEDAI-2K, S2K RI-50, PGA over time.
10. The percent change in serological activity (eg, ANA, anti-dsDNA, other autoantibodies, C3, C4) or SLEDAI feature measurements over time.
11. [redacted]

Medications:

16. The proportion of subjects with meaningful changes in selected SLE medications from Week 12 through Main Study 8-week Safety Follow-up Visit/Week 48.
17. Change in corticosteroid dose from Week 48 through Week 104 for subjects who participate in the study extension.

Development and analyses of the new endpoint(s) will be included in a separated technical report.

9.3. Pharmacokinetics and Immunogenicity

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

9.3.1. Serum Collection and Handling

Venous blood samples will be collected at the time points shown in the Time and Events Schedule for the determination of serum ustekinumab concentrations and antibodies to ustekinumab. Serum samples will also be collected at the final visit from subjects who terminate study participation early. At visits where PK and immunogenicity will be evaluated, 1 blood draw of sufficient volume can be used. Each sample will be split into 3 aliquots (1 aliquot for serum ustekinumab concentration, 1 aliquot for antibodies to ustekinumab, and 1 aliquot as a back-up). Samples must be collected before study drug administration at visits when study drug administration is scheduled. The exact dates and times of blood sample collection must be recorded in the laboratory requisition form.

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

9.3.2. Analytical Procedures

Serum samples will be analyzed to determine ustekinumab concentrations using a validated, specific, and sensitive immunoassay method by Sponsor's bioanalytical facility 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.

9.3.3. Immunogenicity Assessments

Antibodies to ustekinumab will be detected using a validated immunoassay method in serum samples collected from all subjects. 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.

9.4. Biomarkers

The collection, preparation, storage and shipment of skin biopsies, blood, serum and urine are detailed in the Time and Events schedule (Table 1) and the Laboratory Manual. Biomarkers may include, but are not limited to, inflammatory markers, RNA, cell surface markers, auto-antibodies, T cell and B cell repertoire, target specific markers, and other categories of biomarkers potentially involved in the development and the progression of lupus.

Serum Analyses

Serum will be analyzed for levels of specific proteins [redacted].

Urine Samples

Urine samples will be evaluated for excreted proteins or other markers believed to have relevance in SLE.

Skin Biopsy Analyses

Skin biopsies will be utilized for cellular, molecular, and gene expression analyses.

Whole Blood Gene Expression Analyses

Whole blood will be collected from all subjects for RNA, flow cytometry (samples from selected sites will be analyzed at central laboratory or other analytical laboratory), T cell and B cell repertoire (nucleic acid analyses [RNA and DNA] for specific T and B cell receptors only) and epigenetics analysis (eg, DNA methylation).

9.5. Pharmacogenomic Evaluations

The DNA samples will be used for research related to this study (CNTO1275SLE2001). Specific genomic testing will be undertaken for consenting subjects (subjects participating in this portion of the study must sign a separate ICF). The procedure will involve taking a blood sample that may be analyzed for specific target genes that may play a role in lupus. Any genomic assessments will be performed in strict adherence to current subject confidentiality standards for genetic testing. Refusal to participate in genomics testing will not result in ineligibility for participation in the rest of the clinical study.

9.6. Serologic Markers

Sample for autoantibodies (including ANA, anti-dsDNA, anti-Smith), complement C3, C4, and other analytes will be collected as described in the Table of Events (Table 1) and Section 9.8 Safety Evaluations (Clinical Laboratory Tests).

9.7. Cutaneous Lupus Substudy

Subjects with cutaneous disease will be evaluated using CLASI scoring. Additionally, subjects with cutaneous disease who consent to participate in the cutaneous lupus substudy will have additional assessments including collection of skin biopsies (optional consent) prior to study agent administration at Week 0 and at Week 24 and/or photographs of a cutaneous lesion or an area of active disease (optional consent) to be performed as shown in the Table of Events (Table 1). There will not be any restrictions on the number of subjects with cutaneous disease who can enroll into either the main study or the cutaneous lupus substudy.

Subjects who consent to the optional biopsy collection will have 2 skin biopsies (4 mm) excised from an active target lesion at Week 0, followed by 2 additional biopsies of the same lesion (regardless of cutaneous disease activity) at Week 24 (Cutaneous Lupus Substudy Manual). Skin biopsies will be utilized for cellular, molecular, and gene expression analyses.

Independent of cutaneous biopsy collection, subjects who participate in the cutaneous lupus substudy will be requested to provide consent for photographs to be collected from an identified

cutaneous lesion or an area of active disease. Consenting subjects with cutaneous lupus unsuitable for biopsy (eg, malar rash or alopecia) may be evaluated by photography. The photographs are for exploratory purposes only. The photographs will be used to assist in a qualitative evaluation of clinical response. The photographs and skin biopsies can target a different area of active disease, but the follow-up photographs or biopsies should re-evaluate the same area of active disease as originally assessed at week 0. 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.

9.8. Safety Evaluations

Safety assessments include vital signs, general physical examinations and skin evaluations (assessed during S2K RI-50 and CLASI evaluations), adverse events, concomitant medication review, pregnancy testing (refer to Section 12.3.3), administration reactions, chemistry and hematology laboratory tests, and antibodies to ustekinumab. Chest x-ray and TB, HIV, hepatitis B, and hepatitis C testing will be required at time of screening (Table 1). Refer to Section 4.1 for tuberculosis screening criteria. Subject diary cards will be used to capture medication changes that occur in between study visits through the main portion of the study.

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

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

Adverse Events

Adverse events (AE) will be reported by the subject (or, when appropriate, by a caregiver) for the duration of the study, and will be followed by the investigator.

Infections

Subjects will be provided an alert card of signs and symptoms for 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 in 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 treatment must be considered. Treatment must be permanently discontinued for subjects who develop an opportunistic infection. 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 no symptoms of infection, may continue study administration after discussion with the study Sponsor.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected according to the Time and Events Schedule (Table 1 and Table 2 for the extended study). The investigator must review the laboratory report immediately upon availability, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. Coomb's direct test, urine dipstick, urine sediment microscopy and urine pregnancy test will be performed by site staff or the local laboratory. With the approval of the study Sponsor, the use of local laboratories may also be allowed in cases where initiation of treatment or safety follow-up is time-critical and the central laboratory results are not expected to be available before the need to provide study agent treatment or if actions need to be taken for safety reasons.

A one-time retest of screening laboratory test(s) analyzed by the central laboratory will be allowed in the event of suspected error in sample collection or analysis performance.

- Hematology Panel

  -hemoglobin
  -hematocrit
  -white blood cell (WBC) count with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils)
  -platelet count
  -CD 19 B-cell analyses during screening only if needed for subjects previously exposed to B–cell depleting therapies (Section 4.1.3)
  -Coomb's direct test (local laboratories, if available)

- 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)

- Coagulation Labs

  -Prothrombin Time
  -Partial Thromboplastin Time
  -International Normalized Ratio

- Serum Chemistry Panel

  -sodium
  -potassium
  -alkaline phosphatase
  -calcium

-chloride
-bicarbonate
-blood urea nitrogen
-creatinine
-glucose
-aldolase (if creatine kinase is elevated at screening then aldolase test at Week 0 and follow-up as needed)
-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 at Central laboratory.
    - Urinary protein/creatinine ratio[9] will be analyzed at the central laboratory using an aliquot of spot urine collected from subjects.
    - Urine Sediment Microscopy (Local Laboratory Assessment using spot urine samples)

      -Red blood cells
      -WBC, with note if urinary tract infection is present/absent
      -epithelial cells
      -crystals
      -Red blood cells, WBC, or heme-granular casts
      -bacteria

- Serum and urine pregnancy testing for women of childbearing potential only
- Viral serology (HIV antibody, HBsAg, anti-HBs, anti-HBc total, and hepatitis C virus antibody)

Vital Signs

Weight and temperature will be assessed. Blood pressure and heart rate measurements will be assessed.

Physical Examination

A full body physical examination will be performed pre-treatment and during the study as shown in Table 1 and Table 2 for the extended study.

9.9. Sample Collection and Handling

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

Refer to the Time and Events Schedule (Table 1 and Table 2 for the extended study) for the timing and frequency of all sample collections.

Instructions for the collection, handling, and shipment of samples are found in the laboratory manual that will be provided for sample collection and handling.

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

A subject who does not enter into the study extension will be considered to have completed the main study if he or she has completed assessments through 16-week safety follow-up of the main study. A subject who has enrolled into the study extension will be considered to have completed the main portion of this study if he or she has completed assessments through the 8-week safety follow-up visit of the main study. Subjects who prematurely discontinue study treatment for any reason before the Week 8 or Week 16 safety follow-up visits (from the main study), will not be considered to have completed the main portion of the study. A subject who has enrolled into the study extension will be considered to have completed the study extension if he or she has completed assessments through Week 120.

10.2. Discontinuation of Study Treatment

If a subject's study treatment must be discontinued before or at Week 40 (for subjects who do not participate in the study extension) or before Week 104 (for subjects who do participate in the study extension), this will not result in automatic withdrawal of the subject from the study and follow-up assessments should be obtained approximately 8 and 16 weeks following the last dose of study agent.

A subject's study treatment **must be permanently discontinued** if any of the following occur:

1. 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.
2. The subject withdraws consent for administration of study agent.
3. Pregnancy or planning to become pregnant within the study period or within 16 weeks after the last study agent injection.
4. The initiation of prohibited medications or treatments (as per Section 4.3).
5. 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.
6. An opportunistic infection.
7. The investigator or Sponsor’s medical monitor deems it is in the subject’s best interest.
8. 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 continued screening has a chest radiograph with evidence of current active TB and/or a positive QuantiFERON®-TB Gold test and/or a positive tuberculin skin test result in countries in which the QuantiFERON®-TB Gold is not approved/registered result and/or an indeterminate QuantiFERON®-TB Gold test result on repeat testing, unless active TB can be ruled out and appropriate treatment for latent TB can be initiated either prior to or simultaneously with the next administration of study agent and continued to completion.
- A subject receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.

9. Significant worsening of SLE disease activity from baseline or having high disease activity for 2 or more consecutive visits starting at Week 16 based on overall clinical assessments; or if a subject requires the addition of a new immunomodulator to the existing treatment regimen after Week 16.

In addition, permanent discontinuation of study agent treatment **must be considered** for subjects who:

- Receive an increase (relative to baseline) in their immunomodulator dose.
- Develop any of the following adverse events that are reported as serious or severe: study agent infusion reaction, injection-site reaction, or infection.

10.3. 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

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented.

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

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 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 (or appropriate designee)

of withdrawal of consent for the optional research samples and to request sample destruction. The Sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the Sponsor that the samples have been destroyed.

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

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

Withdrawal from the Use of Samples in Future Research

The 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 Statistical Analysis Plan.

11.1. Subject Information

For all subjects who receive at least 1 dose of study drug descriptive statistics will be provided for demographic data and baseline characteristics, including prior and background SLE therapies. All subjects who are randomized and received at least 1 dose of study agent will be included in the efficacy analyses according to their assigned treatment group. The safety analysis population will include those subjects who received at least 1 dose of study agent, and will be analyzed according to the actual study agent received.

11.2. Sample Size Determination

The sample size calculation is based upon the primary endpoint, proportion of SRI-4 responders at Week 24. Approximately 60 subjects treated with ustekinumab and approximately 40 subjects with placebo is projected to give approximately 80% power to detect a significant difference in response rate compared with placebo (assume 35% and 60% response rates in placebo and ustekinumab respectively, which translates to 25% absolute increase over placebo or an odds ratio of 2.79) with an alpha level of 0.1. The assumption of a 35% responder rate for placebo is based upon a previous study in which a similar SLE population was treated.[36] Recent studies have shown very high placebo rates in certain regions, thus the power for the study could be reduced.[14]

The power to detect a significant treatment difference at α=0.1 (2-sided) is calculated under various assumptions (see Table 4).

Table 4: Power to Detect a Significant Treatment Difference in the Proportion of Subjects with SRI-4 Response at Week 24

Proportion of Placebo Group with Response (%)	Absolute Increase in Response (%)	Proportion of Ustekinumab Group with Response (%)	Odds Ratio	Power
20	20	40	2.67	70%
	25	45	3.27	85%
	30	50	4.00	94%
25	20	45	2.45	67%
	25	50	3.00	82%
	30	55	3.67	92%
30	20	50	2.33	64%
	25	55	2.85	80%
	30	60	3.50	91%
35	20	55	2.27	62%
	25	60	2.79	79%
	30	65	3.45	91%
40	20	60	2.25	62%
	25	65	2.79	79%
	30	70	3.50	91%

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

11.3. Efficacy Analyses

All efficacy analyses will be performed on the modified intent-to-treat (mITT) analysis set. The mITT analysis set will include all subjects who are randomized and received at least 1 dose of study agent. The efficacy analyses will be calculated according to their assigned treatment group.

11.3.1. Primary Endpoint Analysis

The primary endpoint of this study is the proportion of subjects with a composite measure of SLE disease activity (SRI-4 response) at Week 24 (Section 9.2.2.1). The primary analysis will be based upon the primary endpoint and will be conducted on the mITT population, which includes all randomized subjects who receive at least 1 dose of study agent, have at least 1 measurement prior to the administration, and have at least 1 post-baseline SRI-4 measurement.

Last observation carried forward procedure will be used to impute the missing SRI-4 component if the subjects have data for at least 1 SRI-4 component at Week 24. If the subjects do not have data for any SRI components at Week 24, the subjects will be considered not to have achieved the SRI-4 response. In addition, subjects who meet any 1 of the following criteria will be considered to have not achieved the primary endpoint, SRI-4 response at Week 24 (full details will be provided in the SAP):

- Between the Week 12 visit and the Week 24 visit, either the dose of an immunomodulator is higher than at baseline, or a new immunomodulator has been added to the existing treatment regimen.
- The addition of a new immunomodulator to the existing treatment regimen before Week 12 and subject still was receiving that immunomodulator after Week 12.

- Initiate treatment with disallowed dose or disallowed use of oral, IV or IM or other type of corticosteroid administration for SLE, or increase the dose of oral corticosteroids for SLE above baseline between the Week 12 and 24 visits.
- Subjects who were not receiving ARB or ACE inhibitor therapy who then initiated a new ARB or ACE inhibitor therapy between Week 12 and Week 24. Subjects who substitute an ARB or ACE inhibitor for a comparable medication would not be considered treatment failures.
- Discontinue study agent due to lack of efficacy for an AE of worsening of SLE prior to Week 24.

For subjects who use systemic corticosteroids for another indication, the efficacy measurement will be carried forward from the last observation prior to the initiation of the treatment, for the period of 2 weeks after initiation of the treatment. After the 2 week period, the subject's calculated value will be as measured.

Other situations may confound the primary endpoint, such as a subject initiating NSAIDs after Week 16, or using epidural, IV, IM, IA, or intra-lesional, inhaled corticosteroids, and topical medication. Data handling rules will be specified in the Statistical Analysis Plan.

Logistic regression, adjusting for baseline stratifications and baseline SLEDAI, will be used to analyze the primary endpoint. The baseline SLEDAI value is defined as the closest non-missing measurement taken prior to the Week 0 infusion. If significant non-normality is observed, appropriate nonparametric tests will be used to evaluate the differences between treatments.

The study will be considered positive if the primary analysis achieves statistical significance at a significance level of 0.1 (2-sided) and ustekinumab shows a positive treatment effect relative to placebo treatment.

In addition to the primary analysis, sensitivity analyses will be performed to explore the effects with different data handling rules. If it is deemed necessary, the primary endpoint will be analyzed on the per protocol population. Details of the inclusion/exclusion rules for per protocol population will be provided in the SAP.

Subgroup analysis based on region will 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 will be presented. Details will be outlined in the SAP.

11.3.2. Major Secondary Analyses

- The change from baseline in SLEDAI-2K at Week 24.
- The change from baseline in PGA at Week 24.
- The proportion of subjects with BICLA response at Week 24.

Continuous responses will be analyzed using an analysis of covariance model with treatment group as a fixed factor and baseline stratifications (eg, regions) as a covariate. Nonparametric methods will be adopted when the normality assumption is violated.

11.3.3. Other Planned Efficacy Analyses

For the other efficacy endpoints listed in Section 9.2.3, the following statistical methods will be applied:

Binary data will be analyzed using the same statistical method as in the primary efficacy analysis. Continuous responses will be analyzed using an analysis of covariance model with treatment group as a fixed factor and baseline stratifications (eg, regions) as a covariate. Nonparametric methods will be adopted when the normality assumption is violated. Log-rank tests will be used to compare endpoints defined by time to an event.

11.3.4. Efficacy Analyses in the Study Extension

Long-term evaluations of efficacy including SRI-4, SLEDAI-2K, PGA, reduction in corticosteroid dosing, and evaluations of flare over time will also be performed for those subjects who participate in the study extension.

11.4. Interim Analyses

Interim analyses (IA) will be conducted when approximately 1/3 and 2/3 of subjects reach Week 24. In the first IA, only evidence for notable efficacy will be assessed. In the second IA, evidence for notable efficacy as well as treatment futility will be analyzed. Variations in placebo effect across regions will be incorporated into the interim analyses. Details concerning the IAs are described in the IA Statistical Analysis Plan.

11.5. Pharmacokinetic Analyses

Serum ustekinumab concentrations will be summarized for each treatment group over time. Descriptive statistics, including arithmetic mean, standard deviation, median, interquartile range, minimum, and maximum will be calculated at each sampling time point.

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

11.6. Immunogenicity Analyses

The incidence and titers of antibodies to ustekinumab will be summarized for subjects who received at least 1 administration 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).

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

11.7. Biomarker Analyses

The following results from treated and untreated SLE subjects will be summarized:

- The concentration of individual serum and urine markers.
- Results from selected biomarkers in skin biopsy tissue by RNA-sequencing and immunohistochemistry.
- Results from whole blood gene expression profiling, flow cytometry, T cell and B cell repertoire, and epigenetics.
- Additional exploratory analyses may be performed following evaluation of the data.

The samples collected from other ongoing clinical studies may also be included in the biomarker data analyses. Results of biomarker analyses may be presented in a separate report.

11.8. Pharmacogenetics Analyses

The DNA research may consist of the analysis of 1 or more candidate genes or of the analysis of genetic markers throughout the genome (as appropriate) in relation to this study.

Results of genomic analyses will be presented in a separate report once the overall number of samples including those collected from other sources is appropriate.

11.9. Pharmacokinetic and Pharmacodynamic Analysis

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

11.10. Safety Analyses

Safety analyses will be based on the population of subjects who received at least 1 dose of either study agent; subjects will be summarized by the treatment they actually received.

Adverse Events

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities. All reported AEs with onset during the treatment phase (ie, treatment-emergent AEs, and AEs that have worsened since baseline) will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. Routine safety evaluations will be performed. Adverse events, serious AEs (SAEs), reasonably related AEs, and AEs by severity will be summarized by treatment group.

The incidence and types of infections, infusion reaction, and inject site reactions will be analyzed for this study. An infusion reaction is defined as an AE that occurs during or within 1 hour following the infusion of study agent, with the exception of laboratory abnormalities.

Special attention will be given to those subjects who died, or who discontinued treatment due to an adverse event, or who experienced a severe or a serious adverse event(eg, summaries, listings, and narrative preparation may be provided, as appropriate).

Clinical Laboratory Tests

Laboratory data will be summarized by the type of laboratory test. Reference ranges and Common Terminology Criteria for Adverse Events (CTCAE) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point. Changes from baseline results will be presented in pre-versus post-treatment cross-tabulations (with classes for below, within, and above normal ranges based on laboratory reference ranges). The baseline is defined as the last measurement prior to the first dose of the randomized treatment. The number and percentage of subjects by Maximum CTCAE Grade will be summarized for each treatment group for each laboratory analyte. The laboratory parameters and change from baseline in selected laboratory parameters (hematology and chemistry), and the number of subjects with abnormal laboratory parameters (hematology and chemistry) based on CTCAE toxicity grading will be summarized treatment group. Listings of SAEs will also be provided. All safety analyses will be based on the population of subjects who received at least 1 dose of either study agent; subjects will be summarized by the treatment they actually received.

Urine protein and creatinine measurements will be used to calculate the urine protein to creatinine ratio. Descriptive statistics will be calculated for these ratios at baseline and at each scheduled time point.

Vital Signs

Vital sign measures at each scheduled time point and their changes from baseline will be summarized using descriptive statistics. The baseline is defined as the last measurement prior to the first dose of the randomized treatment.

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 and to conduct interim efficacy analysis. The committee will meet at least twice to review interim data, including when 1/3 and 2/3 of subjects reach Week 24. After each review, the DMC will make a recommendation to the Sponsor committee whether the study should be stopped for safety concerns. In the first IA, Sponsor will also be notified for notable efficacy in order to advance to next trial. In the second IA, Sponsor will be notified for notable efficacy as well as futility. The details will be provided in a separate DMC charter and in the IA Statistical Plan.

The DMC will have 3 to 6 members who are independent of the Sponsor. The DMC will consist of at least 1 medical expert in the relevant therapeutic area and at least 1 statistician. The DMC responsibilities, authorities, and procedures will be documented in its charter.

The DMC will no longer be active after the assessment of the primary endpoint in this study.

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.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

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 International Conference on Harmonisation [ICH])

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

Note: The Sponsor collects adverse events 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
- 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 1 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 drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction.

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 ustekinumab with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

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.

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 drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a Sponsor study drug
- Suspected abuse/misuse of a Sponsor study drug
- Inadvertent or accidental exposure to a Sponsor study drug
- Medication error involving a Sponsor product (with or without subject/patient exposure to the Sponsor study drug, eg, name confusion)
- Adverse events of special interest: any newly identified malignancy, 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 trial 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.

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

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 drug, 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.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the CRF. 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 CRF 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 serious adverse events that are unlisted (unexpected) and associated with the use of the study drug. The investigator (or Sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

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, which must be completed and signed by a physician from the study site, and transmitted to the Sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made 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 drug 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 the course of 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 CRF).

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

12.3.3. Pregnancy

All initial reports of pregnancy 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. This includes subject report of a positive home over-the-counter pregnancy test. Abnormal pregnancy outcomes (eg, spontaneous abortion, stillbirth, and congenital anomaly) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further study treatment, and followed for 4 months after last study dose.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

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

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 on 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 on the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug

14.1.1. IV administration

Ustekinumab 5 mg/mL FVP (IV) is supplied as 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 EDTA disodium salt, dihydrate at pH 6.0. No preservatives are present.

Placebo for FVP (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, 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.

14.1.2. SC administration

Ustekinumab will also be supplied as a single-use latex-free 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.

14.3. Labeling

Study drug 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 36°F to 46°F (2°C to 8°C), not frozen, and protected from light. 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 of 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 Investigational Product manual for additional guidance on study agent preparation and handling.

14.5. Drug Accountability

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

Study drug 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 drug, and study drug 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 drug, or used returned study drug for destruction, will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

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

Study drug 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 drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug 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 Brochure
- Package Insert for Ustekinumab
- Study site investigational product procedures manual
- Central Laboratory manual
- Cutaneous lupus substudy manual
- Investigational Product manual
- PRO questionnaires and efficacy worksheets
- IWRS manual

- Sample ICF
- Subject diary card

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.

The total blood volume to be collected will be approximately 640 mL per subject over the course of the study, which is approximately 1.5 times the amount of a typical blood donation.

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
- Subject diary card
- 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), 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 samples 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 drug
- 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. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).
- 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

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the Sponsor and by the reviewing IEC/IRB and be in a language that the 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 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 is authorizing such access, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

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

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

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 alteration 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 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.

Exploratory DNA, pharmacodynamic, biomarker, PK and immunogenicity research 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 exploratory research. Therefore, exploratory 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 for PK, immunogenicity and biomarker analyses in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand 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 Study [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, 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 IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate Sponsor representative (see Contact Information page(s) provided separately). 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 CRF 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 drug 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 Food and Drug Administration 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the Sponsor before enrollment of the first 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. 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 documentation must be available for the following to confirm data collected in the CRF: 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 drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

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

- Race
- History of smoking
- Blood pressure, temperature, and pulse/heart rate
- Height and weight

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.1.3, 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.

17.5. Case Report Form Completion

Case report forms are provided for each subject in [electronic format].

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF (eCRF), and transmitted in a secure manner to the Sponsor within the timeframe agreed upon between the Sponsor and the study site. The electronic file will be considered to be the eCRF.

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 documentation. All data relating to the study must be recorded in eCRFs prepared by the Sponsor. Data must be entered into eCRFs in English. Study site personnel must complete the eCRF 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. The investigator must verify that all data entries in the eCRFs are accurate and correct.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or study-site personnel must adjust the eCRF (if applicable) and complete the query.

If corrections to the eCRF are needed after the initial entry into the eCRF, this can be done in 3 different ways:

- 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).
- Study site manager can generate a query for resolution by the study-site personnel.
- Clinical data manager can generate a query for resolution by the 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 CRF completion will be provided and reviewed with study-site personnel before the start of the study. The Sponsor will review CRFs 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 CRFs 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 investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

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

17.8. Monitoring

The Sponsor will use a combination of monitoring techniques (central, remote and/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 CRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF 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 documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRFs and source documents 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 documentation 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. It is important that the study data be recorded promptly in order to

facilitate continuous remote monitoring of data, as well as to conduct interim assessments of study futility and/or notable efficacy.

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

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed with the last visit 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 drug 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 and comparison with the CRFs. 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 pharmacogenomic or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the Sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the Sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the Sponsor in connection with the continued development of 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 CRF data from all study sites that participated in the study, and direct transmission of clinical laboratory data from a central laboratory into the Sponsor's database. 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. Results of pharmacogenomic or exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study 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/or disclose the existence of and the results of clinical studies as required by law.

REFERENCES

1. Albrecht J, Taylor L, Berlin JA, et al. The CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index): an outcome instrument for cutaneous lupus erythematosus. J Invest Dermatol. 2005;125(5):889-894.
2. Bennett L, Palucka AK, Arce E, et al. Interferon and granulopoiesis signatures in systemic lupus erythematosus blood. J Exp Med. 2003;197:711–723.
3. Chen XQ, Yu YC, Deng HH, et al. Plasma IL-17A is increased in new-onset SLE patients and associated with disease activity. J Clin Immunol. 2010;30:221–225.
4. Crispín JC, Oukka M, Bayliss G, et al. Expanded double negative T cells in patients with systemic lupus erythematosus produce IL-17 and infiltrate the kidneys. J Immunol. 2008;181:8761–8766.
5. Dahl C, Johansen C, Kragballe K, Olesen AB. Ustekinumab in the treatment of refractory chronic cutaneous lupus erythematosus: a case report. Acta Derm Venereol. 2013;93:368–369.
6. De Souza A, Ali-Shaw T, Strober BE, Franks Jr AG. Successful treatment of subacute lupus erythematosus with ustekinumab. Arch Dermatol. 2011;147: 896–898.
7. Feagan, BG, Sandborn WJ, Gasink C, et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med. 2016;375(20):1946-1960.
8. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum. 1995;38(6):727-735.
9. Fine DM, Ziegenbein M, Petri M, et al. A prospective study of protein excretion using short-interval timed urine collections in patients with lupus nephritis. Kidney Int. 2009;76(12):1284-1288.
10. Furie RA, Petri MA, Wallace DJ, et al. Novel evidence-based systemic lupus erythematosus responder index. Arthritis & Rheumatism. 2009;61(9):1143-1151.
11. Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol. 2002;29(2):288-291.
12. Han JW, Zheng HF, Cui Y, et al. Genome-wide association study in a Chinese Han population identifies nine new susceptibility loci for systemic lupus erythematosus. Nat Genet. 2009;41:1234e7.
13. Hay EM, Bacon PA, Gordon C, et al. The BILAG index: a reliable and valid instrument for measuring clinical disease activity in systemic lupus erythematosus. Quart J Medicine. 1993;86:447-458.
14. Huang X, Hua J, Shen N, Chen S. Dysregulated expression of interleukin-23 and interleukin-12 subunits in systemic lupus erythematosus patients. Mod Rheumatol. 2007;17(3):220-223.
15. Illei, G., Wang, L., Greth, W., & Khamashta, M. (2015). The effect of geography on the efficacy of sifalimumab, an anti-interferon alpha monoclonal antibody, in moderate to severe systemic lupus erythematosus. Gaithersburg: MedImmune. Clin Exp Rheumatol. 2015; 33(3 Suppl.90):abstr P5.10 (11th International Congress on Systemic Lupus Erythematosus, 2-6 September 2015, Vienna, Austria).
16. International Consortium for Systemic Lupus Erythematosus Genetics (SLEGEN), Harley J, Alarcón-Riquelme M, et al. Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PXK, KIAA1542 and other loci. Nat Genet. 2008;40(2):204-210.
17. Isenberg DA, Rahman A, Allen E, et al. BILAG 2004. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. Rheumatology. 2005;44:902-906.
18. Kim HS, Kim I, Kim JO, Bae JS, Shin HD, Bae SC, No association between interleukin 23 receptor gene polymorphisms and systemic lupus erythematosus. Rheumatol Int. 2009;30: 33–38.
19. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale: application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989;46(10);1121-1123.
20. Linker-Israeli M, Deans RJ, Wallace DJ, et al. Elevated levels of endogenous IL-6 in systemic lupus erythematosus. A putative role in pathogenesis. J Immunol. 1991;147:117–123.

21. McHorney CA, Ware JE Jr, Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. 1994;32(1):40-66.

22. Navarra SV, Guzmán RM, Gallacher AE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet. 2011; 377:721–731.

23. Niewold TB, Hua J, Lehman TJA, Harley JB, Crow MK. High serum IFN-α activity is a heritable risk factor for systemic lupus erythematosus. Genes Immuno. 2007, 8(6):492-502.

24. Oh SH, Roh HJ, Kwon JE, et al. Expression of interleukin-17 is correlated with interferon-α expression in cutaneous lesions of lupus erythematosus. Clin Exp Dermatol. 2011;36:512–520.

25. 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.

26. Qiu F, Song L, Yang N, Li X. Glucocorticoid downregulates expression of IL-12 family cytokines in systemic lupus erythematosus patients. Lupus. 2013;22(10):1011-1016.

27. Samsa G, Edelman D, Rothman ML, et al. Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. Pharmacoeconomics. 1999;15(2):141-155.

28. Sánchez E, Rueda B, Callejas JL, et al. Analysis of interleukin-23 receptor (IL23R) gene polymorphisms in systemic lupus erythematosus. Tissue Antigens. 2007;70:233–237.

29. Sestak AL, Fürnrohr BG, Harley JB, Merrill JT, Namjou B. The genetics of systemic lupus erythematosus and implications for targeted therapy. Ann Rheum Dis. 2011;70(S1): i37–i43.

30. Shah K, Lee WW, Lee SH, et al. Dysregulated balance of Th17 and Th1 cells in systemic lupus erythematosus. Arthritis Res Ther. 2010;12:R53.

31. Tanasescu CE, Balanescu P, Balanescu R, et al. IL-17 in cutaneous lupus erythematosus. Eur J Intern Med. 2010;21:202–207.

32. Touma Z, Gladman DD, Ibanez D, Urowitz MB. Development and initial validation of the systemic lupus erythematosus disease activity index 2000 responder index 50. J Rheumatol. 2011; 38:2; doi:10.3899/jrheum.100724.

33. Touma Z, Gladman DD, Urowitz MB. SLEDAI-2K for a 30 day window. Lupus. 2010a;19(1):49-51. Epub 2009 Nov 12.

34. Touma Z, Urowitz M, Ibañez D, Gladman D. SLEDAI-2K 10 days versus SLEDAI-2K 30 days in a cross-sectional and longitudinal evaluation. Lupus. The 9th International Congress on SLE June 24-27 2010c, Vancouver, Canada. Abstract PO2.D.6.

35. Touma Z; Urowitz M, Gladman D. SLEDAI-2K Responder Index-50 (SRI-50). Lupus. The 9th International Congress on SLE June 24-27 2010b, Vancouver, Canada. Abstract PO2.D.7.

36. Van Vollenhoven RF, Petri MA, Cervera R. et al. Belimumab in the treatment of systemic lupus erythematosus: high disease activity predictors of response. Ann Rheum Dis. 2012;71(8):1343-1349.

37. Vincent FB, Northcott M, Hoi A, et al. Clinical associations of serum interleukin-17 in systemic lupus erythematosus. Arthritis Res Ther. 2013;15: R97.

38. Wallace DJ, Strand D, Furie V, et al. Evaluation of Treatment Success in Systemic Lupus Erythematosus Clinical Trials: Development of the British Isles Lupus Assessment Group-based Composite Lupus Assessment Endpoint. Arthritis Rheum. 2011;63 (S10):S885.

39. Wallace DJ. Lupus: The essential clinician's guide. New York, NY: Oxford University Press, Inc; 2008.

40. Ware JE. SF-36 Health Survey Update. Spine. 2000;25(24):3130-3139.

41. Ware JE, Kosinski M, Keller SK. SF-36 Physical and Mental Health Summary Scales: A User's Manual. Boston MA. The Health Institute, 1994.

42. Ware JE Jr, Sherbourne CD. The MOS 36 item short-form health survey (SF 36), I: conceptual framework and item selection. Med Care. 1992;30(6):473-483.

43. Winchester D, Duffin KC, Hansen C. Response to ustekinumab in a patient with both severe psoriasis and hypertrophic cutaneous lupus. Lupus. 2012; 21:1007–1010.

44. Wong CK, Lit LCW, Tam LS, et al. Hyperproduction of IL-23 and IL-17 in patients with systemic lupus erythematosus: implications for Th17-mediated inflammation in auto-immunity. Clin Immunol. 2008;127: 385–393.

45. Yang X, Wang H, Zhao X, et al. Th22, but not Th17 might be a good index to predict the tissue involvement of systemic lupus erythematosus. J Clin Immunol. 2013; 33:767–774.

46. Zhao XF, Pan HF, Yuan H, et al. Increased serum interleukin 17 in patients with systemic lupus erythematosus. Mol Biol Rep. 2010;37:81–85.

ATTACHMENT 1: EFFICACY EVALUATIONS AND ENDPOINTS

Efficacy Evaluations		Description	Composed of Other Assessments
BILAG	British Isles Lupus Assessment Group	Measure of alterations to therapy consisting of 97 questions in 9 organ systems, each put into 1 of 5 categories (A,B,C,D,E) depending on presence of items. Higher scores indicate more disease involvement.	
BICLA	BILAG-based Combined Lupus Assessment	Composite requiring subjects to meet response criteria across the BILAG, PGA and SLEDAI-2K index.	BILAG PGA SLEDAI-2K
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index	Assesses the disease activity and damage caused to the skin for CLE patients. Scored 0-70 for activity and 0-56 for damage with higher scores indicating extremely active Lupus.	
[redacted]	[redacted]	[redacted]	[redacted]
FSS	Fatigue Severity Scale	A 9-item questionnaire designed to assess the severity of fatigue and its impact on daily living. Each item scored from 1-7 with higher score indicating more severe impact. Scored 9-63.	
Pain VAS	Patients Numeric Rating Scale of Pain	Measures the patient's assessment of pain on a visual analogue scale (VAS; 0 to 10 cm). The anchors of the instrument include 0 to represent 'no pain' and 10 to represent 'the worst pain.'	
PGA	Physician's Global Assessment of Disease Activity	Measures the PGA on a VAS scale. Each scored from 0-10 with higher scores indicating worse activity.	
PtGA	Patient's Global Assessment of Disease Activity	Measures the PtGA on a VAS scale. Each scored from 0-10 with higher scores indicating worse activity.	
SF-36	RAND Short-Form-36 Health Survey	Measures 36 items within 8 health domains. Scored 0-100 for each health concept with higher scores indicating an improved health state. In addition, health concepts can be combined into either a physical or mental component, also scored 0-100.	
SLEDAI-2K (Baseline)	Systemic Lupus Erythematosus Disease Activity Index 2000	Measures 24 features in 9 organ domains over the previous 30 days. Scored 0-105 with higher scores indicating more disease activity.	

S2K RI-50 (Follow-up)	SLEDAI-2K Responder Index 50	Measures clinically important 50% reduction in SLEDAI-2K score.	SLEDAI-2K
SRI-4	SLE Responder Index-4	Composite endpoint requiring at least a 4 point reduction in SLEDAI 2K, no worsening (<10 mm increase) from baseline in PGA and no new BILAG Domain A and no more than 1 new BILAG Domain B scores (see Section 9.2.2.1.).	SLEDAI-2K PGA BILAG
SRI-5 and SRI-6	SLEDAI 2-K SLE Responder Index-5 and SLEDAI 2-K SLE Responder Index-6	Same criteria as SRI-4 however the SRI-5 and SRI-6 require at least a 5 point or 6 point reduction in SLEDAI-2K respectively.	SLEDAI-2K PGA BILAG

ATTACHMENT 2: QUANTIFERON®-TB GOLD TESTING

The QuantiFERON®-TB Gold test is one of the interferon-γ (IFN-γ) based blood assays for TB screening (Cellestis, 2009). It utilizes the recently identified *M. tuberculosis*-specific antigens ESAT-6 and CFP-10 in the standard format, as well as TB7.7 (p4) in the In-Tube format, to detect in vitro cell-mediated immune responses in infected individuals. The QuantiFERON®-TB Gold assay measures the amount of IFN-γ produced by sensitized T cells when stimulated with the synthetic *M. tuberculosis*-specific antigens. In *M. tuberculosis*-infected persons, sensitized T lymphocytes will secrete IFN-γ in response to stimulation with the *M. tuberculosis*-specific antigens and, thus, the QuantiFERON®-TB Gold test should be positive. Because the antigens used in the test are specific to *M. tuberculosis* and not found in BCG, the test is not confounded by BCG vaccination, unlike the tuberculin skin test. However, there is some cross-reactivity with the 3 Mycobacterium species, *M. kansasii*, *M. marinum*, and *M. szulgai*. Thus, a positive test could be the result of infection with one of these 3 species of Mycobacterium, in the absence of *M. tuberculosis* infection.

In a study of the QuantiFERON®-TB Gold test (standard format) in subjects with active TB, sensitivity has been shown to be approximately 89% (Mori et al, 2004). Specificity of the test in healthy BCG-vaccinated individuals has been demonstrated to be more than 98%. In contrast, the sensitivity and specificity of the tuberculin skin test was noted to be only about 66% and 35% in a study of Japanese patients with active TB and healthy BCG-vaccinated young adults, respectively. However, sensitivity and specificity of the tuberculin skin test depend on the population being studied, and the tuberculin skin test performs best in healthy young adults who have not been BCG-vaccinated.

Data from a limited number of published studies examining the performance of the QuantiFERON®-TB Gold assay in immunosuppressed populations suggest that the sensitivity of the QuantiFERON®-TB Gold test is better than the tuberculin skin test even in immunosuppressed patients (Ferrara et al, 2005; Kobashi et al, 2007; Matulis et al, 2008). The ability of IFN-γ-based tests to detect latent infection has been more difficult to study due to the lack of a gold standard diagnostic test; however, several TB outbreak studies have demonstrated that the tests correlated better than the tuberculin skin test with the degree of exposure that contacts had to the index TB case (Brock et al, 2004; Ewer et al, 2003). In addition, TB contact tracing studies have shown that patients who had a positive QuantiFERON®-TB Gold test result and were not treated for latent TB infection were much more likely to develop active TB during longitudinal follow-up than those who had a positive tuberculin skin test and a negative QuantiFERON®-TB Gold test result (Higuchi et al, 2007; Diel et al, 2008).

Although the performance of the new IFN-γ-based blood tests for active or latent *M. tuberculosis* infection have not been well validated in the immunosuppressed population, experts believe these new tests will be at least as, if not more, sensitive, and definitely more specific, than the tuberculin skin test (Barnes, 2004; personal communication, April, 2008 TB Advisory Board).

Performing the QuantiFERON®-TB Gold In Tube Test

The QuantiFERON®-TB Gold test In-Tube format will be provided for this study. The In-Tube format contains 1 additional *M. tuberculosis*-specific antigen, TB7.7 (p4), which is thought to increase the specificity of the test.

To perform the test using the In-Tube format, blood is drawn through standard venipuncture into supplied tubes that already contain the *M. tuberculosis*-specific antigens. Approximately 3 tubes will be needed per subject, each requiring 1 mL of blood. One tube contains the *M. tuberculosis*-specific antigens, while the remaining tubes contain positive and negative control reagents. Thorough mixing of the blood with the antigens is necessary prior to incubation. The blood is then incubated for 16 to 24 hours at 37°C, after which tubes are centrifuged for approximately 15 minutes at 2000 to 3000g. Following centrifugation, plasma is harvested from each tube, frozen, and shipped on dry ice to the central laboratory. The central

laboratory will perform an ELISA to quantify the amount of IFN-γ present in the plasma using spectrophotometry and computer software analysis.

The central laboratory will analyze and report results for each subject, and sites will be informed of the results. Subjects who have an indeterminate result should have the test repeated.

Adherence to Local Guidelines

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.

In countries in which the QuantiFERON®-TB Gold test is not considered approved/registered, a tuberculin skin test is additionally required.

References

Barnes PF. Diagnosing latent tuberculosis infection: Turning glitter to gold [editorial]. Amer J Respir Crit Care Med. 2004;170:5-6.

Brock I, Weldingh K, Lillebaek T, et al. Comparison of tuberculin skin test and new specific blood test in tuberculosis contacts. Am J Respir Crit Care Med. 2004;170:65-69.

Cellestis. QuantiFERON-TB Gold clinicians guide and QuantiFERON-TB Gold In-Tube Method package insert. Downloaded from www.cellestis.com, February 2009.

Diel R, Loddenkemper R, Meywald-Walter K, Niemann S, Nienhaus A. Predictive value of a whole blood IFN-λ assay for the development of active tuberculosis disease after recent infection with mycobacterium tuberculosis. Am J Respir Crit Care Med. 2008;177:1164-1170.

Ewer K, Deeks J, Alvarez L, et al. Comparison of T-cell-based assay with tuberculin skin test for diagnosis of Mycobacterium tuberculosis infection in a school tuberculosis outbreak. Lancet. 2003;361:1168-73.

Ferrara G, Losi M, Meacci M, et al. Routine hospital use of a new commercial whole blood interferon-γ assay for the diagnosis of tuberculosis infection. Am J Respir Crit Care Med. 2005; 172:631-635.

Higuchi K, Nobuyuki H, Mori T, Sekiya Y. Use of QuantiFERON-TB Gold to investigate tuberculosis contacts in a high school. Respirology. 2007;12:88-92.

Kobashi Y, Mouri K, Obase Y, et al. Clinical evaluation of QuantiFERON-TB-2G test for immunocompromised patients. Eur Respir J. 2007; 30:945-950.

Matulis G, Jüni P, Villiger PM, Gadola SD. Detection of latent tuberculosis in immunosuppressed patients with autoimmune diseases: performance of a Mycobacterium tuberculosis antigen-specific interferon λ assay. Ann Rheum Dis. 2008;67:84-90

Mori T, Sakatani M, Yamagishi F, et al. Specific detection of tuberculosis infection: An interferon-γ-based assay using new antigens. Am J Respir Crit Care Med. 2004;170:59-64.

ATTACHMENT 3: TUBERCULIN SKIN TESTING

Administering the Mantoux Tuberculin Skin Test

The Mantoux tuberculin skin test (CDC, 2000) is the standard method of identifying persons infected with Mycobacterium tuberculosis. Multiple puncture tests (Tine and Heaf) should not be used to determine whether a person is infected because the amount of tuberculin injected intradermally cannot be precisely controlled. Tuberculin skin testing is both safe and reliable throughout the course of pregnancy. The Mantoux tuberculin test is performed by placing an intradermal injection of 0.1 mL of tuberculin into the inner surface of the forearm. The test must be performed with tuberculin that has at least the same strength as either 5 tuberculin units (TU) of standard purified protein derivative (PPD) S or 2 TU of PPD RT 23, Statens Seruminstitut, as recommended by the World Health Organization. PPD strengths of 1 TU or 250 TU are not acceptable (Menzies, 2000). Using a disposable tuberculin syringe with the needle bevel facing upward, the injection should be made just beneath the surface of the skin. This should produce a discrete, pale elevation of the skin (a wheal) 6 mm to 10 mm in diameter. To prevent needle-stick injuries, needles should not be recapped, purposely bent or broken, removed from disposable syringes, or otherwise manipulated by hand. After they are used, disposable needles and syringes should be placed in puncture-resistant containers for disposal. Institutional guidelines regarding universal precautions for infection control (eg, the use of gloves) should be followed. A trained health care worker, preferably the investigator, should read the reaction to the Mantoux test 48 to 72 hours after the injection. 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

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

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

ATTACHMENT 4: HBV SCREENING AND MONITORING

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):

1) Subjects who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) ***are eligible*** for this study.
2) 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.
3) Subjects who test **positive only** for **surface antibody** (anti-HBs+) ***are eligible*** for this study.
4) Subjects who test **positive** for surface antigen (HBsAg+) ***are NOT eligible*** for this study, regardless of the results of other hepatitis B tests.
5) 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: SLEDAI-2K/S2K RI-50 AT SCREENING VISIT

Data retrieval sheet for SLEDAI-2K/S2K RI-50 at Screening Visit

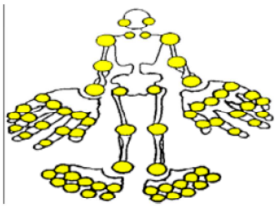
Descriptors present at the time of the visit or the preceding 30 days

SCREENING VISIT	Circle Score	
	Present	Absent
Seizure ☐Partial (focal, local) seizures ☐simple partial seizures (consciousness not impaired) ☐complex partial (with impairment of consciousness) ☐partial seizures (simple or complex) evolving to secondarily generalized seizures ☐Generalized seizures ☐nonconvulsive (absence) ☐convulsive **Days per month** _____	8	0
Psychosis ☐Altered ability to function in normal activity due to: ☐hallucinations ☐incoherence ☐marked loose associations ☐impoverished thought content ☐marked illogical thinking ☐bizarre, disorganized or catatonic behavior	8	0
Organic brain syndrome ☐Altered mental function (with rapid onset and fluctuating clinical features) with impaired: ☐orientation ☐memory ☐other intellectual function ☐clouding of consciousness with reduced capacity to focus and inability to sustain attention to environment ☐perceptual disturbance ☐incoherent speech ☐insomnia or daytime drowsiness ☐increased or decreased psychomotor activity	8	0
Visual ☐cytoid bodies ☐retinal hemorrhage ☐serous exudates in the choroid ☐hemorrhage in the choroid ☐optic neuritis	8	0
Cranial nerve disorder Nerves involved _____ ☐motor power_____ ☐sensory deficit_____ ☐pain as determined by patient on numerical scale of 1-10*_____	8	0
Lupus headache ☐pain as determined by patient on numerical scale of 1-10*_____	8	0
CVA Clinical diagnosis:_____ Date of CVA (yyyy/mm/dd)_____ ☐face ☐upper extremities ☐lower extremities ☐motor power_____ ☐sensory deficit location:_____	8	0

* Numerical scale: 1 is minimal and 10 is most severe

S2K RI-50, Screening Visit, Version 3, 01-August-2012 (University Health Network)
Adapted by Janssen R&D 21 Oct 2015

REVIEW COPY

Vasculitis ☐ ulceration of _____ ☐ gangrene of _____ Body Surface Area_____% Size of biggest lesion:_____ ☐ periungual infarction # of involved digits _____ ☐ splinter hemorrhages # of involved digits _____ ☐ tender finger nodules # of involved digits _____ ☐ total number of digits involved (including hand and feet) # of involved digits _____ _____	**8**	**0**
SCREENING VISIT	**Circle Score**	
	Present	Absent
Arthritis		
Total Number of joints with pain and signs of inflammation (ie tenderness, swelling or effusion) # total _____. Note: joints with both pain and inflammation should only be counted as a single joint	**4**	**0**
 Number of joints with tenderness (pain) # _____		
 Number of joints with swelling or effusion # _____		
Myositis Motor power_____considering also lab results for creatinine phosphokinase level _____and aldolase_____	**4**	**0**
Urinary casts (if analysis is available at study site) ☐ Number of heme-granular casts _____and / or ☐ Number of red blood cells casts_____ *(check box)*	**4**	**0**
Hematuria: (if analysis is available at study site) Number of red blood cells/high power field_____	**4**	**0**
Proteinuria : Level of proteinuria_____	**4**	**0**
Pyuria: (if analysis is available at study site) : Number of white blood cells/high power field_____	**4**	**0**

* Numerical scale: 1 is minimal and 10 is most severe

S2K RI-50, Screening Visit, Version 3, 01-August-2012 (University Health Network)
Adapted by Janssen R&D 21 Oct 2015

REVIEW COPY

Rash ☐head ☐chest ☐abdomen ☐ back ☐ legs ☐arms/hands ☐mucous membrane Body Surface Area_____% Number of lesions:_____ Size of biggest lesion:_____ Activity of most active skin lesion by color: ☐absent ☐pink, faint erythema ☐red ☐ ☐dark/purple/violaceous/crusted/hemorrhagic Dyspigmentation, scarring and atrophy are not active lesions	**2**	**0**
Alopecia ☐patchy total scalp area involved:_____% size of biggest lesion:_____ ☐diffuse alopecia as determined by patient on numerical scale of 1-10*_____ Activity of alopecia by color based on most active lesion: ☐ absent ☐ pink, faint erythema ☐red ☐dark/purple / violaceous/ crusted / hemorrhagic	**2**	**0**
Mucosal ulcers Number of ulcers per month_____	**2**	**0**
Pleurisy ☐pain as determined by patient on numerical scale of 1-10* _____ Amount of effusion if determined radiologically_____	**2**	**0**
Pericarditis ☐pain as determined by patient on numerical scale of 1-10* _____ Amount of effusion if determined radiologically _____	**2**	**0**
Low complement C3_____C4_____	**2**	**0**
DNA_____	**2**	**0**
Fever T ^{0}C (mean)_____	**1**	**0**
Thrombocytopenia Platelet count _____	**1**	**0**
Leucopenia WBC count _____	**1**	**0**
TOTAL SCORE		

REVIEW COPY

* Numerical scale: 1 is minimal and 10 is most severe

S2K RI-50, Screening Visit, Version 3, 01-August-2012 (University Health Network)
Adapted by Janssen R&D 21 Oct 2015

ATTACHMENT 6: SLEDAI-2K / S2K RI-50 (BASELINE)

Data retrieval sheet for SLEDAI-2K/S2K RI-50 at Baseline Visit (Week 0)

Descriptors present at the time of the visit or the preceding 30 days

BASELINE VISIT (WEEK 0)	Circle Score	
	Present	Absent
Seizure. ☐Partial (focal, local) seizures ☐simple partial seizures (consciousness not impaired) ☐complex partial (with impairment of consciousness) ☐partial seizures (simple or complex) evolving to secondarily generalized seizures ☐Generalized seizures ☐nonconvulsive (absence) ☐convulsive **Days per month** _____	8	0
Psychosis ☐Altered ability to function in normal activity due to: ☐hallucinations ☐incoherence ☐marked loose associations ☐impoverished thought content ☐marked illogical thinking ☐bizarre, disorganized or catatonic behavior	8	0
Organic brain syndrome ☐Altered mental function (with rapid onset and fluctuating clinical features) with impaired: ☐orientation ☐memory ☐other intellectual function ☐clouding of consciousness with reduced capacity to focus and inability to sustain attention to environment ☐perceptual disturbance ☐incoherent speech ☐insomnia or daytime drowsiness ☐increased or decreased psychomotor activity	8	0
Visual ☐cytoid bodies ☐retinal hemorrhage ☐serous exudates in the choroid ☐hemorrhage in the choroid ☐optic neuritis	8	0
Cranial nerve disorder Nerves involved _____ ☐motor power _____ ☐sensory deficit _____ ☐pain as determined by patient on numerical scale of 1-10* _____	8	0
Lupus headache ☐pain as determined by patient on numerical scale of 1-10* _____	8	0
CVA Clinical diagnosis:_____ Date of CVA (yyyy/mm/dd) _____ ☐face ☐upper extremities ☐lower extremities ☐motor power_____ ☐sensory deficit location: _____	8	0

REVIEW COPY

* Numerical scale: 1 is minimal and 10 is most severe

**Lab results to be included when received after week 0 visit, however not considered in Wk 0 scoring for SLEDAI score ≥ 4 just prior to randomization.

S2K RI-50, Baseline Visit, Version 3, 01-August-2012 (University Health Network) Page 1

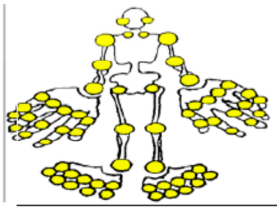
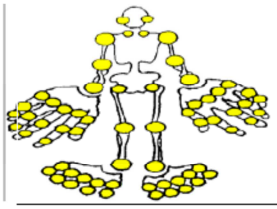
Adapted by Janssen R&D 21 Oct 2015, Baseline Visit (Week 0)

Vasculitis ☐ ulceration of _____ ☐ gangrene of _____ Body Surface Area_____% Size of biggest lesion:_____ ☐ periungual infarction # of involved digits _____ ☐ splinter hemorrhages # of involved digits _____ ☐ tender finger nodules # of involved digits _____ ☐ total number of digits involved (including hand and feet) _____	**8**	**0**

REVIEW COPY

* Numerical scale: 1 is minimal and 10 is most severe

**Lab results to be included when received after week 0 visit, however not considered in Wk 0 scoring for SLEDAI score ≥ 4 just prior to randomization.

BASELINE VISIT (WEEK 0)	Circle Score	
	Present	Absent
Arthritis		
Total Number of joints with pain and signs of inflammation (ie tenderness, swelling or effusion) # total _____. *Note: joints with both pain and inflammation should only be counted as a single joint*	4	0
 Number of joints with tenderness (pain) #_____		
 Number of joints with swelling or effusion #_____		
Myositis Motor power_____considering also lab results for creatinine phosphokinase level_____ and aldolase_____**	4	0
Urinary casts (if analysis is available at study site) ** ☐Number of heme-granular casts _____and / or ☐Number of red blood cells casts_____ *(check box)*	4	0
Hematuria: (if analysis is available at study site)** Number of red blood cells/high power field_____	4	0
Proteinuria: Level of proteinuria_____	4	0
Pyuria: (if analysis is available at study site) _____ Number of white blood cells / high power field: _____	4	0
Rash ☐head ☐chest ☐abdomen ☐back ☐legs ☐arms/hands ☐mucous membrane Body Surface Area_____%Number of lesions: _____ Size of biggest lesion: _____ Activity of most active skin lesion by color: ☐absent ☐pink, faint erythema ☐red ☐dark/purple/violaceous/crusted/hemorrhagic Dyspigmentation, scarring and atrophy are not active lesions	2	0

REVIEW COPY

* Numerical scale: 1 is minimal and 10 is most severe

**Lab results to be included when received after week 0 visit, however not considered in Wk 0 scoring for SLEDAI score ≥ 4 just prior to randomization.

Alopecia ☐patchy total scalp area involved: _____% size of biggest lesion: _____ ☐diffuse alopecia as determined by patient on numerical scale of 1-10* _____ Activity of alopecia by color based on most active lesion: ☐absent ☐pink, faint erythema ☐red ☐dark/purple / violaceous/ crusted / hemorrhagic	**2**	**0**
Mucosal ulcers Number of ulcers per month_____	**2**	**0**
Pleurisy ☐pain as determined by patient on numerical scale of 1-10* _____ Amount of effusion if determined radiologically _____	**2**	**0**
Pericarditis ☐pain as determined by patient on numerical scale of 1-10* _____ Amount of effusion if determined radiologically_____	**2**	**0**
Fever T °C (mean) _____	**1**	**0**
Thrombocytopenia** Platelet count _____	**1**	**0**
Leucopenia** WBC count _____	**1**	**0**
TOTAL CLINICAL SCORE at Wk 0 (without Lab data)		

REVIEW COPY

* Numerical scale: 1 is minimal and 10 is most severe

**Lab results to be included when received after week 0 visit, however not considered in Wk 0 scoring for SLEDAI score ≥ 4 just prior to randomization.

ATTACHMENT 7: S2K RI-50 (FOLLOW-UP)

Data retrieval sheet of SLEDAI-2K / S2K RI-50 Follow Up Visit

Descriptors are present at the time of the visit or the preceding 30 days, comparison is to Baseline Result

FOLLO W UP VISIT	Circle Score Improvement Relative to Baseline (Wk 0)		
	< 50%	≥ 50%	100% ** (Complete recovery)
Seizure ☐Partial (focal, local) seizures ☐simple partial seizures (consciousness not impaired) ☐complex partial (with impairment of consciousness) ☐partial seizures (simple or complex) evolving to secondarily generalized seizures ☐Generalized seizures ☐nonconvulsive (absence) ☐convulsive **Days per month _____**	8	4	0
Psychosis ☐Altered ability to function in normal activity due to: ☐hallucinations ☐incoherence ☐marked loose associations ☐impoverished thought content ☐marked illogical thinking ☐bizarre, disorganized or catatonic behavior **Percentage of improvement of the acute event _____%**	8	4	0
Organic brain syndrome ☐Altered mental function (with rapid onset and fluctuating clinical features) with impaired: ☐orientation ☐memory ☐other intellectual function ☐clouding of consciousness with reduced capacity to focus and inability to sustain attention to environment ☐perceptual disturbance ☐incoherent speech ☐insomnia or daytime drowsiness ☐increased or decreased psychomotor activity **Percentage of improvement of the acute event _____%**	8	4	0
Visual ☐cytoid bodies ☐retinal hemorrhage ☐serous exudates in the choroid ☐hemorrhage in the choroid ☐optic neuritis **Percentage of improvement of the retinal exam _____%**	8	4	0

REVIEW COPY

* Numerical scale: 1 is minimal and 10 is most severe

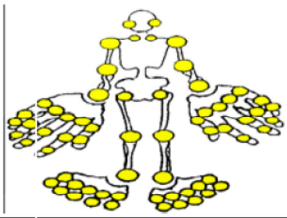
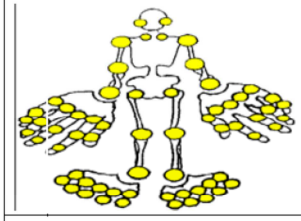
**100% improvement recorded if feature is completely improved OR if there is absence of a feature that was absent at baseline

Cranial nerve disorder Nerves involved _____ ☐motor power _____ **Percentage of improvement of the acute event _____%** ☐sensory deficit _____ **Percentage of improvement of the acute event _____%** ☐pain as determined by patient on numerical scale of 1-10* _____	**8**	**4**	**0**
Lupus headache ☐ pain as determined by patient on numerical scale of 1-10* _____	**8**	**4**	**0**
CVA Clinical diagnosis:_____ Date of CVA (yyyy/mm/dd) _____ ☐face ☐upper extremities ☐lower extremities ☐motor power ☐sensory deficit location: **Percentage of improvement of the acute event _____%**	**8**	**4**	**0**
Vasculitis ☐ulceration of _____ ☐gangrene of _____ Body Surface Area_____% Size of biggest lesion:_____ ☐ periungual infarction # of involved digits _____ ☐ splinter hemorrhages # of involved digits _____ ☐ tender finger nodules # of involved digits _____ ☐ total number of digits involved (including hand and feet) # of involved digits _____ _____	**8**	**4**	

REVIEW COPY

* Numerical scale: 1 is minimal and 10 is most severe

**100% improvement recorded if feature is completely improved OR if there is absence of a feature that was absent at baseline

FOLLOW UP VISIT	Score (Circle) Improvement Relative to Baseline (Wk 0)		
	< 50%	≥ 50%	100% **
Arthritis			
Total Number of joints with pain and signs of inflammation (ie tenderness, swelling or effusion) # total _____. *Note: joints with both pain and inflammation should only be counted as a single joint*	4	2	0
 Number of joints with tenderness**(pain)** # _____			
 Number of joints with swelling or effusion # _____			
Myositis Motor power_____ considering also lab results for creatinine phosphokinase level_____ and aldolase_____	4	2	0
Urinary casts (if analysis is available at study site) ☐ Number of heme-granular casts _____and / or ☐ Number of red blood cells casts_____ *(check box)*	4	2	0
Hematuria: (if analysis is available at study site) Number of red blood cells / high power field: _____	4	2	0
Proteinuria (if analysis is available at study site) Level of proteinuria	4	2	0
Pyuria: (if analysis is available at study site) Number of white blood cells / high power field: _____	4	2	0

PREVIEW

* Numerical scale: 1 is minimal and 10 is most severe

**100% improvement recorded if feature is completely improved OR if there is absence of a feature that was absent at baseline

Rash ☐head ☐chest ☐abdomen ☐back ☐legs ☐arms/hands ☐mucous membrane Body Surface Area_____% Number of lesions: _____ Size of biggest lesion: _____ Activity of most active skin lesion by color: ☐absent ☐pink, faint erythema ☐red ☐dark/purple/violaceous/crusted / hemorrhagic Dyspigmentation, scarring and atrophy are not active lesions	**2**	**1**	**0**
Alopecia ☐patchy total scalp area involved:_____% size of biggest lesion:_____ ☐diffuse alopecia as determined by patient on numerical scale of 1-10*_____ Activity of alopecia by color based on most active lesion: ☐absent ☐pink, faint erythema ☐red ☐dark/purple / violaceous/ crusted / hemorrhagic	**2**	**1**	**0**
Mucosal ulcers Number of ulcers per month_____	**2**	**1**	**0**
Pleurisy ☐pain as determined by patient on numerical scale of 1-10* _____ Amount of effusion if determined radiologically_____	**2**	**1**	**0**
Pericarditis ☐pain as determined by patient on numerical scale of 1-10* _____ Amount of effusion if determined radiologically_____	**2**	**1**	**0**
Fever T °C (mean) T °C (mean)_____	**1**	**0.5**	**0**
Thrombocytopenia platelet count_____	**1**	**0.5**	**0**
Leucopenia WBC count_____	**1**	**0.5**	**0**

REVIEW COPY

* Numerical scale: 1 is minimal and 10 is most severe

**100% improvement recorded if feature is completely improved OR if there is absence of a feature that was absent at baseline

ATTACHMENT 8: BILAG 2004

BILAG-2004 INDEX Date: Site: Patient No: DOB:

- **Only record manifestations/items due to SLE Disease Activity**
- **Assessment refers to manifestations occurring in the last 4 weeks (compared with the previous 4 weeks)**
- **TO BE USED WITH THE GLOSSARY**

Record: **ND Not Done**
0 Not present
1 Improving
2 Same
3 Worse
4 New
Yes/No OR Value (where indicated)
***Y/N Confirm this is due to SLE activity (Yes/No)**

CONSTITUTIONAL
1. Pyrexia - documented > 37.5ºC ( )
2. Weight loss - unintentional > 5% ( )
3. Lymphadenopathy/splenomegaly ( )
4. Anorexia ( )

MUCOCUTANEOUS
5. Skin eruption - severe ( )
6. Skin eruption - mild ( )
7. Angio-oedema - severe ( )
8. Angio-oedema - mild ( )
9. Mucosal ulceration - severe ( )
10. Mucosal ulceration - mild ( )
11. Panniculitis/Bullous lupus - severe ( )
12. Panniculitis/Bullous lupus - mild ( )
13. Major cutaneous vasculitis/thrombosis ( )
14. Digital infarcts or nodular vasculitis ( )
15. Alopecia - severe ( )
16. Alopecia - mild ( )
17. Peri-ungual erythema/chilblains ( )
18. Splinter haemorrhages ( )

NEUROPSYCHIATRIC
19. Aseptic meningitis ( )
20. Cerebral vasculitis ( )
21. Demyelinating syndrome ( )
22. Myelopathy ( )
23. Acute confusional state ( )
24. Psychosis ( )
25. Acute inflammatory demyelinating polyradiculoneuropathy ( )
26. Mononeuropathy (single/multiplex) ( )
27. Cranial neuropathy ( )
28. Plexopathy ( )
29. Polyneuropathy ( )
30. Seizure disorder ( )
31. Status epilepticus ( )
32. Cerebrovascular disease (not due to vasculitis) ( )
33. Cognitive dysfunction ( )
34. Movement disorder ( )
35. Autonomic disorder ( )
36. Cerebellar ataxia (isolated) ( )
37. Lupus headache - severe unremitting ( )
38. Headache from IC hypertension ( )

MUSCULOSKELETAL
39. Myositis - severe ( )
40. Myositis - mild ( )
41. Arthritis (severe) ( )
42. Arthritis (moderate)/Tendonitis/Tenosynovitis ( )
43. Arthritis (mild)/Arthralgia/Myalgia ( )

Weight (kg):	**Serum urea (mmol/l):**
African ancestry: Yes/No	**Serum albumin (g/l):**

CARDIORESPIRATORY
44. Myocarditis - mild ( )
45. Myocarditis/Endocarditis + Cardiac failure ( )
46. Arrhythmia ( )
47. New valvular dysfunction ( )
48. Pleurisy/Pericarditis ( )
49. Cardiac tamponade ( )
50. Pleural effusion with dyspnoea ( )
51. Pulmonary haemorrhage/vasculitis ( )
52. Interstitial alveolitis/pneumonitis ( )
53. Shrinking lung syndrome ( )
54. Aortitis ( )
55. Coronary vasculitis ( )

GASTROINTESTINAL
56. Lupus peritonitis ( )
57. Abdominal serositis or ascites ( )
58. Lupus enteritis/colitis ( )
59. Malabsorption ( )
60. Protein losing enteropathy ( )
61. Intestinal pseudo-obstruction ( )
62. Lupus hepatitis ( )
63. Acute lupus cholecystitis ( )
64. Acute lupus pancreatitis ( )

OPHTHALMIC
65. Orbital inflammation/myositis/proptosis ( )
66. Keratitis - severe ( )
67. Keratitis - mild ( )
68. Anterior uveitis ( )
69. Posterior uveitis/retinal vasculitis - severe ( )
70. Posterior uveitis/retinal vasculitis - mild ( )
71. Episcleritis ( )
72. Scleritis - severe ( )
73. Scleritis - mild ( )
74. Retinal/choroidal vaso-occlusive disease ( )
75. Isolated cotton-wool spots (cytoid bodies) ( )
76. Optic neuritis ( )
77. Anterior ischaemic optic neuropathy ( )

RENAL
78. Systolic blood pressure (mm Hg) value ( ) **Y/N***
79. Diastolic blood pressure (mm Hg) value ( ) **Y/N***
80. Accelerated hypertension Yes/No ( )
81. Urine dipstick protein (+=1, ++=2, +++=3) ( ) **Y/N***
82. Urine albumin-creatinine ratio mg/mmol ( ) **Y/N***
83. Urine protein-creatinine ratio mg/mmol ( ) **Y/N***
84. 24 hour urine protein (g) value ( ) **Y/N***
85. Nephrotic syndrome Yes/No ( )
86. Creatinine (plasma/serum) µmol/l ( ) **Y/N***
87. GFR (calculated) ml/min/1.73 m^2 ( ) **Y/N***
88. Active urinary sediment Yes/No ( )
89. Active nephritis Yes/No ( )

HAEMATOLOGICAL
90. Haemoglobin (g/dl) value ( ) **Y/N***
91. Total white cell count (x 10^9/l) value ( ) **Y/N***
92. Neutrophils (x 10^9/l) value ( ) **Y/N***
93. Lymphocytes (x 10^9/l) value ( ) **Y/N***
94. Platelets (x 10^9/l) value ( ) **Y/N***
95. TTP ( )
96. Evidence of active haemolysis Yes/No ( )
97. Coombs' test positive (isolated) Yes/No ( )

Revision: 1/Sep/2009

ATTACHMENT 9: CLASI

Cutaneous LE Disease Area and Severity Index (CLASI)

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

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

Mucous membrane

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

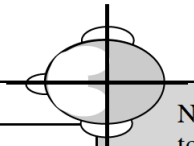
Dyspigmentation

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

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

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

Alopecia



Recent Hair loss (within the last 30 days / as reported by patient) 1-Yes 0-No		NB: if scarring and non-scarring aspects seem to coexist in one lesion, please score both

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

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

Total Activity Score		Total Damage Score	
(For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrophy, Mucous membrane involvement and Alopecia)		(For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation, Scarring/Atrophy/Panniculitis and Scarring of the Scalp)	

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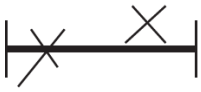
ATTACHMENT 10: PHYSICIAN GLOBAL ASSESSMENT OF DISEASE ACTIVITY

PHYSICIAN'S GLOBAL ASSESSMENT OF DISEASE ACTIVITY

Was the questionnaire completed? ..... ❑Yes ❑No, ***(specify)*** _____

For answering the following questions we have supplied you with a horizontal line. The ends of the horizontal line represent the very best and the very worst situation. Please put a single vertical line across the horizontal line at the spot that you feel best reflects the answer to the question (at the ends or somewhere in between). You must complete this form independently at each visit. Therefore, you MUST NOT review your prior assessments when completing the current PGA.

DON'T



DO

How do you assess your patient's current Lupus?

no Lupus activity — extremely active Lupus

Physician's Signature:_____ Date: __ __ - __ __ __ - 2 0 __ __
day month year

ATTACHMENT 11: PATIENTS GLOBAL ASSESSMENTS OF DISEASE AND PAIN ACTIVITY

PATIENT ASSESSMENT

For answering the following questions, we have supplied you with a horizontal line. The ends of the horizontal line represent the very best and the very worst situation. Please put a single vertical line across the horizontal line at the spot that you feel best reflects the answer to the question (at the ends or somewhere in between). You must complete this form independently at each visit. Therefore, you MUST NOT review your prior assessments when completing current assessments.

1. Patient's Assessment of Pain

On average, how much pain have you had because of your condition in the past week?

2. Patient's Global Assessment of Disease Activity

Considering all the ways your Lupus affects you, on average, how have you been doing in the past week?

ATTACHMENT 12: SF-36

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h	Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i	Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

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4. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the <u>kind</u> of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities <u>less carefully than usual</u>	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

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ATTACHMENT 13: FATIGUE SEVERITY SCALE

Fatigue Severity Scale (FSS) - U.S. English

The Fatigue Severity Scale (FSS) is a method of evaluating the impact of fatigue on you. The FSS is a short questionnaire that requires you to rate your level of fatigue.

The FSS questionnaire contains nine statements that rate the severity of your fatigue symptoms. Read each statement and circle a number from 1 to 7, based on how accurately it reflects your condition during the past week and the extent to which you agree or disagree that the statement applies to you.

- **A low value (e.g., 1) indicates strong disagreement with the statement, whereas a high value (e.g., 7) indicates strong agreement.**
- **It is important that you circle a number (1 to 7) for every question.**

FSS Questionnaire	Disagree ← → Agree						
During the past week, I have found that:							
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my three most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

Scoring your results

Now that you have completed the questionnaire, it is time to score your results and evaluate your level of fatigue. It's simple: Add all the numbers you circled to get your total score.

The Fatigue Severity Scale key

A total score of less than 36 suggests that you may not be suffering from fatigue.

A total score of 36 or more suggests that you may need further evaluation by a physician.

Your next steps

This scale should not be used to make your own diagnosis.

If your score is 36 or more, please share this information with your physician. Be sure to describe all your symptoms as clearly as possible to aid in your diagnosis and treatment.

Fatigue Severity Scale © Lauren B. Krupp. Reproduced with permission from the author.

INVESTIGATOR AGREEMENT

Stelara® (ustekinumab)

Clinical Protocol CNTO1275SLE2001 Amendment 3

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): Elizabeth Hsia, MD

Institution: Janssen Research & Development

Signature: [redacted] Date: 18 Jan 2017

(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.

148

Approved, 18 January 2017