A PHASE 2, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF CC-220 IN SUBJECTS WITH ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS

PROTOCOL NUMBER:	**CC-220-SLE-002**
DATE FINAL:	**23 Feb 2017**
AMENDMENT 1	**18 Jun 2018**
AMENDMENT 2	**15 Aug 2018**
EudraCT NUMBER:	**2016-004574-17**
IND NUMBER:	**116088**
SPONSOR NAME/ ADDRESS:	Celgene Corporation [redacted]

CONFIDENTIAL

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MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

PROTOCOL SUMMARY

Study Title

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Study to Evaluate the Efficacy and Safety of CC-220 in Subjects with Active Systemic Lupus Erythematosus

Indication

Systemic Lupus Erythematosus (SLE)

Objectives

- Primary Objective:
  - To evaluate the clinical efficacy of three doses of CC-220 (0.45 mg once per day [QD], 0.3 mg QD or 0.15 mg QD) compared to placebo, for the treatment of active SLE using the SLE Responder Index at Week 24
- Secondary Objectives:
  - To evaluate additional measures of clinical disease activity of CC-220 (0.45 mg once per day [QD], 0.3 mg QD or 0.15 mg QD) compared to placebo for the treatment of subjects with active SLE at Week 24
  - To assess the reduction in steroid use
  - To assess the reduction in fatigue
  - To evaluate the safety and tolerability of three doses of CC-220 (0.45 mg QD, 0.3 mg QD, and 0.15 mg QD) compared to placebo in subjects with active SLE

Study Design

CC-220-SLE-002 is a Phase 2, randomized, placebo-controlled, double-blind, parallel group study with three active treatment groups (see Figure 1 for study design and Section 5 for Table of Events).

The study consists of 5 phases:

- Screening Phase up to 5 weeks
- Randomized, Double-Blind, Placebo-Controlled Phase of up to 24 weeks
- Randomized, Double-Blind, Active Treatment Phase of up to 28 weeks
- Long-term Extension Phase of up to 52 weeks
- Observational Follow-up Phase of 4 weeks for females and 12 weeks for males

The total duration of the study is 113 weeks for females and 121 weeks for males. The total duration of the treatment period is 104 weeks.

Approximately 280 subjects will be randomized 2:2:1:2 to receive CC-220 (0.45 mg QD, 0.3 mg QD or 0.15 mg QD) or identically appearing placebo. There will be approximately 80 subjects randomized into the CC-220 0.45 mg QD and 0.3 mg QD dosing arms; 40 subjects randomized into the CC-220 0.15 mg QD dosing arm; and approximately 80 subjects in the placebo arm using an Interactive Response Technology (IRT). The treatment assignment will be stratified by Baseline corticosteroid dose (≥ 10 mg/d and < 10 mg/d) and screening SLEDAI 2K score (≥ 10 points and < 10 points).

At Week 24, all placebo subjects will be re-randomized 1:1 in a blinded fashion by IRT to either CC-220 0.45 mg QD or 0.3 mg QD. All subjects who were initially randomized to CC-220 (0.45 mg QD, 0.3 mg QD, or 0.15 mg QD) will be blindly re-randomized by IRT to the same dose group to which they were originally assigned. Once an optimal dose is identified by the Sponsor, subjects who have reached Week 24 will be transitioned to that dose. If more than one dose is identified for further investigation, subjects will be re-randomized accordingly as per the IRT. Subjects who complete the 52-week treatment phase may be eligible for enrollment into a long-term extension phase of up to 52 weeks in duration.

The study will be conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practices (GCPs).

Study Population

Subjects are required to:

- Have a diagnosis of SLE for at least 6 months prior to the Screening Visit and fulfill the 1997 update of the 1982 American College of Rheumatology (ACR) (Appendix E) Classification Criteria for SLE at the Screening Visit.
- Have a SLEDAI 2K (Appendix B) score of ≥ 6 points at the Screening Visit at least 4 points of which are a "clinical" SLEDAI 2K score.
  - A “clinical” score is the SLEDAI 2K assessment score without the inclusion of points attributed to any urine or blood laboratory results including immunologic measures.
- Have a “clinical” SLEDAI 2K (Section 3.1) score of ≥ 4 points at the Baseline Visit

- Have at least one of the following positive antibodies per the central laboratory within the Screening Phase:
  - Positive antinuclear antibody (ANA) test with a titer of ≥ 1:40, associated with a diagnosis of SLE,
  - Anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies elevated to above normal,
  - Anti-Smith (anti-Sm) antibody elevated to above normal.

  A positive ANA test from a local qualified laboratory performed in the last 6 months prior to or during the Screening Phase may be accepted for study entry and will be reviewed by the adjudication committee for eligibility purposes.
- Enter the study on standard of care medications for SLE including antimalarials, immunosuppressants, and/or corticosteroids.

Subjects eligibility for enrollment will be adjudicated during the Screening Phase and prior to Randomization. The SLE disease activity measures will be adjudicated throughout the trial.

Length of Study

The length of study participation is 113 weeks for females and 121 weeks for males. This includes a 5-week Screening Phase, 52-week Treatment Phase, 52-week Long-term Extension Phase and a 4-week Observational Follow-Up Phase with an additional 12-week Observational Follow-Up Visit for males.

The End of Trial is defined as either the date of the last visit of the last subject to complete the posttreatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

Study Treatments

Subjects will be assigned to either CC-220 0.45 mg QD, CC-220 0.3 mg QD, CC-220 0.15 mg QD or placebo using 2:2:1:2 randomization ratio. Subjects assigned to the placebo group will receive matching placebo capsule(s) daily.

If a subject discontinues investigational product (IP) early (ie, prior to completing Visit 15 during the core study or prior to completing Visit 28 during the Long-term Extension study), they will be required to complete an Early Termination Visit as soon as possible and enter into a 4-week Observational Follow-up Phase with an additional 12-week Observational Follow-up Visit for males. In addition, if a subject completes through Visit 15, but opts not to enter the Long-term Extension Phase or completes the Long-term Extension Phase, the subject will enter into a 4-week Observational Follow-up Phase with an additional 12-week Observational Follow-up Visit for males.

Overview of Key Efficacy Assessments

- SLE Responder Index consists of:
  - Systemic Lupus Erythematosus Disease Activity Index 2K (SLEDAI 2K) (Appendix B)

  - British Isles Lupus Assessment Group 2004 (BILAG) (Appendix C)
  - Physician's Global Assessment (PGA) (Appendix G)
- Cutaneous Lupus Area and Severity Index (CLASI) (Appendix D)
- Swollen and Tender Joint Counts (Appendix F)
- Systemic Lupus International Collaborating Clinics/American College of Rheumatology Systemic Lupus Erythematosus (SLICC/ACR SLE) Damage Index (Appendix M)
- BILAG-Based Composite Lupus Assessment (BICLA)
- Lupus Low Disease Activity State (LLDAS)
- Short Form-36 (SF-36) (Appendix N)
- Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale (Appendix H)
- Lupus patient reported outcome (LupusPRO™) (Appendix K)
- Health assessment questionnaire-disability index (HAQ-DI) (Appendix L)

Overview of Key Safety Assessments

- Adverse events (Section 6.8.1)
- Vital signs (pulse, temperature, and blood pressure) (Section 6.8.2)
- Hematology, chemistry, and urinalysis (Section 6.8.5)
- Urine or serum beta-human chorionic gonadotropin (HCG) pregnancy tests (for females of childbearing potential [FCBP]) (Section 6.8.6)
- 12-lead electrocardiograms (ECGs) (Section 6.8.4)
- Physical examinations, including height and weight (Section 6.8.3)
- Concomitant medications and procedures (Section 6.7.4)
- Hepatitis B and C screening (Section 6.8.8)
- Human Immunodeficiency Virus (HIV) testing (Section 6.8.9)
- Testosterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) **for males only** (Section 6.8.5)
- Chest radiograph (for those subjects who have not had a chest radiograph in the 3 months prior to the Screening Visit) (Section 6.8.11)

Statistical Methods

A two-group chi-square (continuity corrected) test with a 0.1 two-sided significance level will have approximately 80% power to detect a true 21% difference (55% versus 34%) between one of the CC-220 groups and the placebo group, for the proportion of subjects achieving an SLE

Responder Index (SRI)(4) response at Week 24, when the sample size in each treatment group is 80.

The primary efficacy endpoint is the SRI(4) response at Week 24. The proportion of subjects who achieve SRI(4) response at Week 24 in each of the CC-220 0.45 mg QD, 0.3 mg QD or 0.15 mg QD group, will be compared with placebo group using a Cochran-Mantel-Haenszel (CMH) test controlling for corticosteroid dose (≥ 10 mg/d and < 10 mg/d) at Baseline and SLEDAI 2K score (≥ 10 points and < 10 points) at Screening. Missing data for binary endpoints will be handled by nonresponder imputation (NRI), by which a subject will be considered a nonresponder at a given time point if the subject 1) does not have sufficient data (including the baseline data for the endpoints assessing the change from Baseline) assessed within the analysis visit window for response determination, or 2) has had an event of treatment failure (as per the prespecified criteria) before the date of assessment (or the date of the last assessment in the case of a composite endpoint involving multiple criteria that may be assessed on different dates) for the time point.

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2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
– To evaluate the clinical efficacy of three doses of CC-220 (0.45 mg once per day [QD], 0.3 mg QD or 0.15 mg QD) compared to placebo, for the treatment of active systemic lupus erythematosus (SLE) using the SLE Responder Index at Week 24
Secondary Objectives
– To evaluate additional measures of clinical disease activity of CC-220 (0.45 mg once per day [QD], 0.3 mg QD or 0.15 mg QD) compared to placebo for the treatment of subjects with active SLE at Week 24 – To assess the reduction in steroid use – To assess the reduction in fatigue – To evaluate the safety and tolerability of three doses of CC-220 (0.45 mg QD, 0.3 mg QD, and 0.15 mg QD) compared to placebo in subjects with active SLE
[redacted]
[redacted]
[redacted]
[redacted]

Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary	SLE Responder Index (SRI) (4)	Proportion of subjects who achieve SRI(4) response Composite endpoint SRI(4), defined by the following criteria: • Reduction from Baseline of ≥ 4 points in the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) 2K score and • No new one or more British Isles Lupus Assessment Group (BILAG) A or new* 2 or more BILAG B items compared to Baseline using BILAG 2004 Index and • No worsening from Baseline defined by an increase of < 0.30 points from Baseline on a Physician's Global Assessment (PGA) visual analog scale (VAS) from 0-3 *new excludes A to B	Week 24
Secondary	SLEDAI 2K	Proportion of subjects with SLEDAI 2K score improvement of ≥ 4 points from Baseline	Week 24
	CLASI	Proportion of subjects with a ≥ 50% reduction in Cutaneous Lupus Area and Severity Index (CLASI) activity score from Baseline, in subjects with Baseline CLASI activity score ≥ 10	Week 24
	BILAG	No new organ system affected as defined by 1 or more BILAG A or new* 2 or more BILAG B items compared to Baseline using BILAG 2004 Index *new excludes A to B	Week 24
	PGA	Percentage of subjects with no worsening (increase of < 0.30 points from Baseline) in PGA compared to Baseline	Week 24
	Joint Counts	• Mean change from Baseline in swollen joint count in subjects with ≥ 2 swollen joints at Baseline • Mean change from Baseline in tender joint count in subjects with ≥ 2 tender joints at Baseline	Week 24
	PGA	Mean change from Baseline in PGA score	Week 24
	Fatigue	Change from Baseline in Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue score	Week 24

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
	Corticosteroid Reduction	• The percentage of subjects with a prednisone or equivalent dose of ≥ 10 mg/day at Baseline whose prednisone or equivalent dose has been reduced to ≤ 7.5 mg/day by Week 16 and maintained through Week 24 with no flares between Week 16 and Week 24 • The percentage of subjects with a prednisone or equivalent dose of ≥ 10 mg/day at Baseline whose prednisone or equivalent dose has been reduced to < 10 mg/day by Week 16 and maintained through Week 24 with no flares between Week 16 and Week 24 • Percent change from Baseline in oral corticosteroid (OCS) dose in subjects with prednisone or equivalent ≥ 10 mg/day at Baseline • The total corticosteroid dose from Baseline through Week 24	Week 24
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
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Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
	[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
[redacted]	[redacted]	[redacted]	[redacted]
Safety	Safety	Safety and tolerability as defined by the following: • Type, frequency, severity, and relationship of adverse events, clinical laboratory tests including urine cytology, 12-lead ECG, vital signs, and physical examination	Through Week 104
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
[redacted]	[redacted]	[redacted]	[redacted]

3. OVERALL STUDY DESIGN

3.1. Study Design

CC-220-SLE-002 is a Phase 2 randomized, placebo-controlled, double-blind, parallel group study with three active treatment groups (see Figure 1 for study design and Section 5 for Table of Events).

The study consists of 5 phases:

- Screening Phase up to 5 weeks
- Randomized, Double-Blind, Placebo-Controlled Phase of up to 24 weeks
- Randomized, Double-Blind, Active Treatment Phase of up to 28 weeks
- Long-term Extension Phase of up to 52 weeks
- Observational Follow-up Phase of 4 weeks for females and 12 weeks for males

The total duration of the study is 113 weeks for females and 121 weeks for males. The total duration of the treatment period is 104 weeks.

Approximately 280 subjects will be randomized 2:2:1:2 to receive CC-220 (0.45 mg QD, 0.3 mg QD or 0.15 mg QD) or identically appearing placebo. There will be approximately 80 subjects randomized into the CC-220 0.45 mg QD and 0.3 mg QD dosing arms; 40 subjects randomized into the CC-220 0.15 mg QD dosing arm; and approximately 80 subjects in the placebo arm using an Interactive Response Technology (IRT). The treatment assignment will be stratified by Baseline corticosteroid dose (≥ 10 mg/d and < 10 mg/d) and screening SLEDAI 2K score (≥ 10 points and < 10 points) (Furie, 2016).

Subjects will have a documented diagnosis of SLE, meet the ACR Classification Criteria (Appendix E), and meet the SLEDAI 2K entry criteria as described below.

The eligibility criteria require that:

- At the Screening Visit, subjects have a SLEDAI 2K score of ≥ 6 points, WITH at least 4 points being “clinical”. The “clinical” score excludes points attributable to any urine or laboratory results including immunologic measures.
- At the Baseline Visit, subjects must have a “clinical” SLEDAI 2K score of ≥ 4 points. The “clinical” score excludes points attributable to any urine or laboratory results including immunologic measures.

The following SLEDAI 2K criteria qualify as “clinical”:

- Alopecia*
- Vasculitis
- Arthritis
- Myositis
- Rash
- Mucosal ulcers
- Pleurisy
- Pericarditis
- Fever

*Alopecia will count toward the "clinical" SLEDAI 2K score only if the CLASI activity score for alopecia is 2 or 3. Alopecia with a CLASI activity alopecia score of 1, will only count toward the total SLEDAI score.

Subjects with neurological manifestations of lupus are excluded from the study. As such, no neurologic descriptors of the SLEDAI 2K score (items 1 to 7) will be counted towards the SLEDAI study entry criteria. However, neurological manifestations of lupus which occur during the study, must be collected and scored accordingly.

During the screening phase and prior to the Baseline Visit, it is recommended that sites contact subjects to evaluate their concomitant medication. This call will be used to confirm that subjects are not taking any prohibited medications and to ensure that subjects taking any protocol permitted concomitant medications are on an appropriate dose and are maintaining stable dosing according to the protocol.

At Week 24, all remaining placebo subjects will be re-randomized 1:1 in a blinded fashion by IRT to either CC-220 0.45 mg QD or 0.3 mg QD. All subjects who were initially randomized to CC-220 (0.45 mg QD, 0.3 mg QD, or 0.15 mg QD) will be blindly re-randomized by IRT to the same dose group to which they were originally assigned.

Subjects who complete the Treatment Phase may be eligible to roll over into a Long-term Extension of up to 52 weeks in duration. Subjects who enter this phase will maintain the CC-220 dosage they were re-randomized to at Week 24.

To maintain the blind at the site and subject level, the individual subject treatment assignments will not be revealed to the Investigators until after the 52-week database lock and after all final analyses are completed and the final results have been released.

Once an optimal dose is identified, subjects will be transitioned to that dose. If more than one dose is identified for further study, subjects will be re-randomized accordingly as per the IRT.

If a subject discontinues investigational product (IP) early (ie, prior to completing Visit 15 during the Active Treatment Phase or prior to completing Visit 28 during the Long-term Extension), they will be required to complete an Early Termination Visit as soon as possible and enter into a 4-week Observational Follow-up Phase with an additional 12-week Observational Follow-up visit for males. In addition, if a subject completes the Randomized, Double-Blind, Active Treatment Phase, but opts not to enter the Long-term Extension Phase or completes the Long-term Extension Phase, the subject will enter into a 4-week Observational Follow-up Phase with an additional 12-week Observational Follow-up Visit for males.

A 4-week Observational Follow-up Phase is included for all subjects to monitor subject safety after cessation of treatment. An additional 12-week Observational Follow-up Visit is included for males to monitor hormone levels (testosterone, LH, FSH).

The study will be conducted in compliance with the International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

3.1.1. Safety Management Team (SMT)

In addition to daily safety monitoring conducted by Investigators and study personnel, cumulative and interval blinded adverse events (AEs), SAEs, discontinuations, and laboratory

findings will be reviewed by a SMT. The SMT is comprised of lead representatives from multiple Sponsor functions engaged in the CC-220 development program. The scope, conduct, processes, and accountabilities of the SMT are prespecified in a SMT charter.

3.1.2. Independent External Data Monitoring Committee (DMC)

Although Sponsor study staff will monitor safety on an ongoing basis throughout the study, formal blinded safety assessments of the relevant study data will be performed by an external independent Data Monitoring Committee (DMC). The DMC will review unblinded data to evaluate safety during the study and data from the interim analysis for futility. The DMC is comprised of independent physician experts and a statistician for whom there is no identified conflict of interest. The DMC will be convened regularly, at least once a year, or ad hoc at the request of the SMT. Recommendations of the DMC based on the overall benefit/risk evaluation may include proceeding with the study per protocol, proceeding with the study with modification, or study suspension. The scope, conduct, membership, processes, and accountabilities of the DMC are specified in the DMC charter.

3.1.3. Adjudication

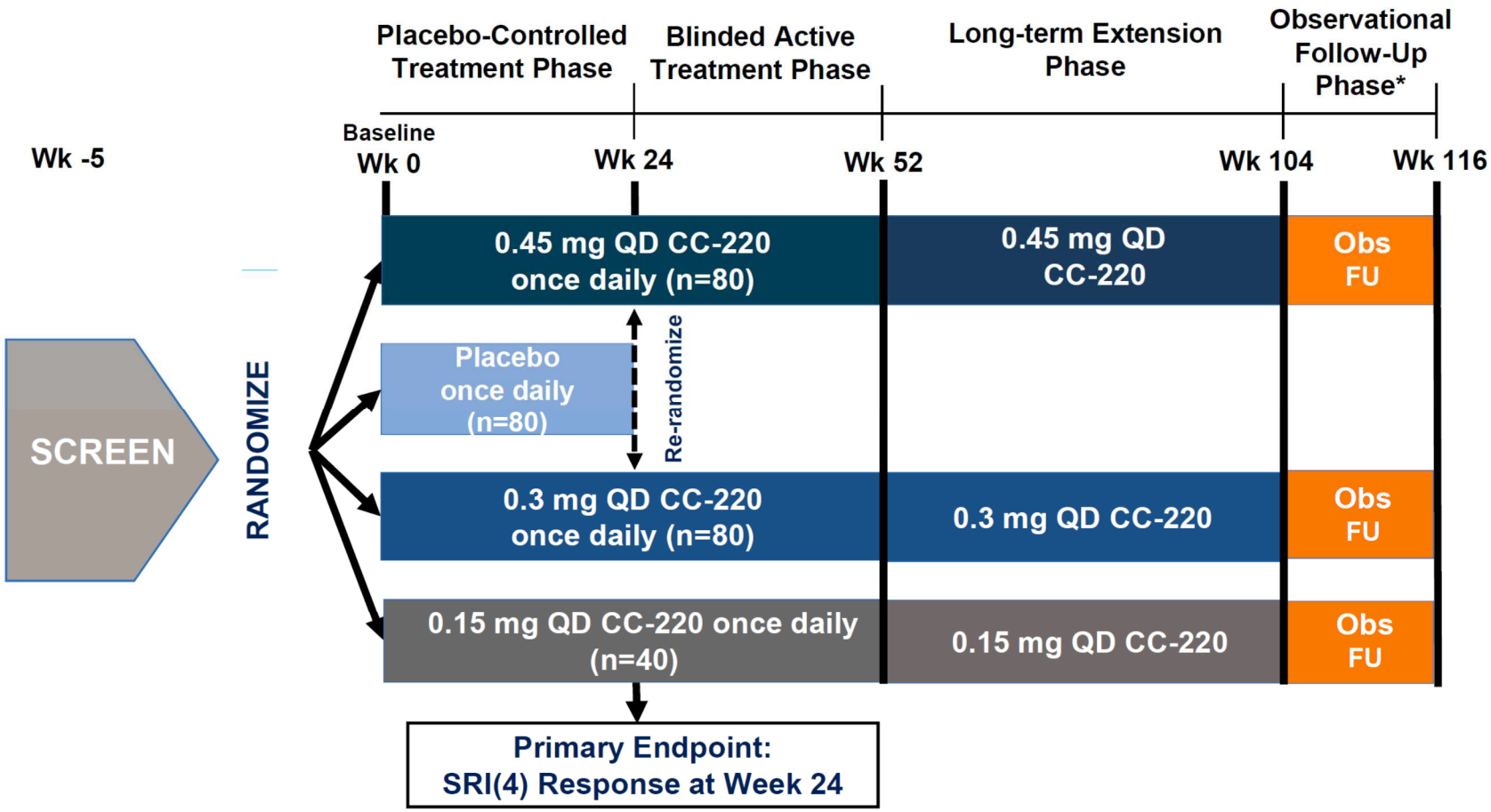
Subjects eligibility for enrollment will be adjudicated during Screening and Randomization. No subject is allowed to be randomized into the study without the approval of the adjudication committee. Additionally, SLE disease activity measures will be adjudicated throughout the trial in a blinded fashion to ensure data quality. Details regarding the adjudication process are specified in a separate charter.

3.1.4. Background Medication

Subjects will be required to be on standard of care medications for SLE, see Section 1.3.2.2. Subjects will remain on oral corticosteroids, immunosuppressants (methotrexate, sulfasalazine, azathioprine, 6-mercaptopurine, mycophenolate mofetil, mycophenolic acid, leflunomide, tacrolimus, cyclosporine) and/or antimalarials (hydroxychloroquine, quinacrine, chloroquine) during the study, as long as they have been treated for at least 4 weeks prior to the Screening Visit and on a stable dose for at least 2 weeks prior to their Baseline Visit for corticosteroids, and/or treated for at least 12 weeks and on a stable dose for at least 8 weeks prior to their Baseline Visit for immunosuppressants/antimalarials (Section 8.1).

See Inclusion Criteria, Section 4.2, and Section 8.1 for details of the allowed dose regimens.

Figure 1: Overall Study Design



Obs FU = Observational Follow Up Phase; QD = once per day; SLE = systemic lupus erythematosus; SRI(4) = SLE Responder Index(4); Wk = week.
*Female subjects will have a 4-week Observational Follow-Up Phase. Males will have a 12-week Observational Follow-Up Phase.

3.2. Study Duration for Subjects

The length of study participation is 113 weeks for females and 121 weeks for males. This includes a 5-week Screening Phase, 52-week Treatment Phase, 52-week Long-term Extension Phase and a 4-week Observational Follow-Up Phase with an additional 12-week Observational Follow-Up Visit for males.

3.3. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the posttreatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

4. STUDY POPULATION

4.1. Number of Subjects

Approximately 280 subjects will be enrolled at multiple (approximately 100) sites globally.

4.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study.

Age/Gender

1. Male or female 18 years of age or older at the time of signing the informed consent.
2. Understand and voluntarily sign informed consent forms (ICFs) prior to the initiation of any study specific assessments/procedures.
3. Able and willing to adhere to the visit schedule and other protocol requirements.

Disease Specific

4. Have a diagnosis of SLE for at least 6 months prior to the Screening Visit and fulfill the 1997 update of the 1982 American College of Rheumatology (ACR) (Appendix E) Classification Criteria for SLE at the Screening Visit.
5. A SLEDAI 2K score of ≥ 6 points, WITH at least 4 points being a "clinical" SLEDAI 2K score. The “clinical” score excludes points attributable to any urine or blood laboratory results including immunologic measures. As subjects with neurological manifestations of lupus are excluded from the study, no neurologic descriptors of the SLEDAI 2K score (items 1 to 7) will be counted towards the SLEDAI study entry criteria (see Appendix B).

   The following SLEDAI 2K criteria qualify as “clinical”:
   - Alopecia*
   - Vasculitis
   - Arthritis
   - Myositis
   - Rash
   - Mucosal ulcers
   - Pleurisy
   - Pericarditis
   - Fever

   * Alopecia will count toward the “clinical” SLEDAI 2K score only if the CLASI activity score for alopecia is 2 or 3 (Appendix D). Alopecia with a CLASI activity alopecia score of 1, will only count toward the total SLEDAI score.
6. At the Baseline Visit, a clinical SLEDAI 2K score of ≥ 4 points.
7. Have at least one of the following positive antibodies associated with SLE per the central laboratory within the Screening Phase:
   - Positive antinuclear antibody (ANA) test with a titer of ≥ 1:40, associated with a diagnosis of SLE,
   - Anti-dsDNA antibodies elevated to above normal,

- Anti-Smith (anti-Sm) antibody elevated to above normal.

A positive ANA test from a local qualified laboratory performed in the last 6 months prior to or during the Screening phase may be accepted for study entry and will be reviewed by the adjudication committee for eligibility purposes.

8. All subjects must receive approval by the adjudication committee (Section 3.1.3) prior to enrollment into the study.

Pregnancy

All male and female subjects should be counseled about pregnancy precautions and risks of fetal exposure as described in the Pregnancy Prevention Plan (provided separately) (Section 6.8.7).

9. Females of childbearing potential (FCBP)[1] must:
   - Have two negative pregnancy tests as verified by the Investigator prior to starting study therapy, one within 10 to 14 days prior to the first dose of CC-220 and again within 24 hours before taking the first dose of CC-220. She must agree to ongoing pregnancy testing during the course of the study, and after end of study treatment. This applies even if the subject practices true abstinence[2] from heterosexual contact.
   - Either commit to true abstinence[2] from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use two forms of reliable contraception simultaneously. One must be on a highly effective method and one additional effective (barrier) method (Section 6.8.7), and both must be practiced without interruption, 28 days prior to starting investigational product, during the study therapy (including dose interruptions), and for 28 days after discontinuation of study therapy.
10. Male subjects must: Practice true abstinence[2] or agree to use a barrier contraception (male latex condom or non-latex condom NOT made out of natural [animal] membrane [for example, polyurethane]) during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 90 days following investigational product discontinuation, even if he has undergone a successful vasectomy.
11. Male subjects must agree not to donate semen or sperm during therapy and for at least 90 days following the discontinuation of IP.
12. All subjects must:
    - Understand that the IP could have potential teratogenic risk.

[1] A female of childbearing potential is a sexually mature female who 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been postmenopausal for at least 24 consecutive months (that is, has had menses at any time during the preceding 24 consecutive months).

[2] True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).

- Agree to abstain from donating blood while taking IP and for 28 days following discontinuation of the IP.
- Agree not to share IP with another person.
- Other than the subject, FCBP and males able to father a child should not handle the IP or touch the capsules unless gloves are worn.
- Be counseled about pregnancy precautions and risks of fetal exposure as described in the Pregnancy Prevention Plan.

[redacted]

For Long-term Extension Phase only:

18. Subjects have completed participation in the placebo-controlled and active treatment study phases.

    Subjects eligibility to enter the long-term extension phase will be dependent on the ongoing adjudication review.

4.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment. In the event one or more of the laboratory criteria is not satisfied due to unexpected or unexplained reason, subjects may repeat the respective laboratory or ECG test one time during the Screening Phase.

If the result(s) do not satisfy eligibility criteria, subjects will be ineligible to enroll in the study and will be considered a screen failure. **Subjects may be re-screened twice with the approval of the medical monitor**.

Concomitant Medications and Procedures

1. The subject has received immunomodulating or immunosuppressive therapy (except corticosteroids and permitted medications described in inclusion criterion 13 or Section 8), such as:
    a. Cyclophosphamide within 6 months of the Baseline Visit. Previous use of Melphalan or other alkylating agents is prohibited.
    b. Etanercept within 8 weeks prior to the Baseline Visit.
    c. Belimumab within 3 months prior to the Baseline Visit.
    d. B-cell depleting or modulating agents, such as rituximab or anti-CD22 therapy, within 1 year prior to the Baseline Visit.
    e. Any other biologic or non-biologic immunosuppressive agent within 2 months of 5 pharmacokinetic half-lives (whichever is longer) prior to the Baseline Visit.
2. The subject has been treated with intra-articular, intralesional, subcutaneous, intradermal, intramuscular or IV pulse corticosteroids 6 weeks prior to the Baseline Visit.
3. The subject has received high potency topical or intralesional corticosteroids, topical immunosuppressants, and/or retinoids within 2 weeks of the Screening Visit (only Class 6 or 7 are permitted [Section 8.1.2.3]).
4. The subject has undergone plasmapheresis within 3 months of the Baseline Visit.
5. The subject has received IV immunoglobulin within 3 months of the Baseline Visit.
6. The subject has participated in a clinical trial and has received an investigational product within 5 pharmacokinetic half-lives or 2 months, (whichever is longer) prior to the Baseline Visit.
7. The subject has received strong inhibitors or inducers of CYP3A4/5, including grapefruit, St. John's Wort or related products within two weeks prior to the Baseline Visit (Please refer to Appendix I for examples of medications).
8. The subject has a planned or received immunization with a live or live attenuated vaccine within 2 months prior to the Baseline Visit and for 2 months after administration of the last dose of IP.

Disease Severity

9. The subject has an estimated glomerular filtration rate (eGFR) of < 45 mL/min/1.7 m^2 or proteinuria > 2000 mg/day based on protein to creatinine ratio, or has active lupus

nephritis that in the opinion of the adjudication committee may require 'induction' therapy.

10. The subject has active, severe or unstable neuropsychiatric lupus disease (e.g., poorly controlled seizure disorder, acute confusional state, myelitis, stroke or stroke syndrome, cerebellar ataxia or dementia related to SLE, psychosis, organic brain syndrome, cerebrovascular accident [CVA], cerebritis or central nervous system [CNS] vasculitis), within 6 months of the Screening Visit. Please contact Medical Monitor if further clarification is needed.

Concomitant Disease

11. The subject has QTcF of > 450 milliseconds on the screening ECG.
12. The subject has serologic tests during Screening (see Section 6.8.8) consistent with infection with either hepatitis B or hepatitis C, and/or confirmed history of hepatitis B or hepatitis C infection. Subjects with isolated positive hepatitis B surface antibody are not excluded.
13. The subject has a history of congenital and/or acquired immunodeficiencies or any underlying condition that predisposes the subject to infection, or a positive laboratory test for HIV infection during Screening (unless prohibited by local health authority or IRB/EC requirements).
14. The subject has active or history of recurrent bacterial, viral, fungal, mycobacterial or other infections (including, but not limited to, atypical mycobacterial disease and herpes zoster). The subject has any major episode of infection requiring hospitalization or treatment with intravenous or oral antibiotics within 4 weeks of the Screening Visit and at any time during the Screening Phase, up through the first dose of IP. Subjects with minor infections that meet these criteria may be discussed with the medical monitor for approval for study entry.
15. The subject has a history of latent or active TB, unless there is medical record documentation of successful completion of a standard course of treatment per local guidelines. The subject has a QuantiFERON®-TB Gold test result at Screening elevated to above normal as per the central laboratory, unless there is medical record documentation of successful completion of a standard course of treatment per local guidelines. Indeterminate QuantiFERON®-TB Gold test results should be repeated and if the result is indeterminate again then the subject should not be enrolled, unless there is medical record documentation of successful completion of a standard course of treatment per local guidelines.
16. The subject has an abnormal chest radiograph with evidence of active infection or possible malignancy. A chest radiograph should be taken prior to the Baseline Visit, when most of the eligibility criteria are met, so that results are available prior to the Baseline Visit. A posterior-anterior (PA) radiograph is required. A lateral view is strongly recommended unless prohibited by local health authority requirements. Alternatively, PA or PA/lateral radiographs or chest computed tomography (CT) scans that were taken within the 3 months (or longer periods based on local health authority requirements) prior to the Screening Visit will be accepted for evaluation for participation in the study. Note: If screening chest radiograph shows abnormalities with no significant changes from

previous radiographs then the subject may be considered for enrollment. Please contact the medical monitor to discuss prior to entry.

17. The subject has a history of an organ transplant (eg, heart, lung, kidney, liver) or hematopoietic stem cell/marrow transplant. Subjects with other types of transplants may be discussed with the medical monitor for study entry approval.
18. The subject has malignancy or history of malignancy, except for:
    - treated (eg, cured) basal cell or squamous cell in situ skin carcinomas
    - treated (eg, cured) cervical intraepithelial neoplasia Grade 1 and 2
    - treated (eg, cured) carcinoma in situ of the cervix with no evidence of disease within 5 years of the Screening Visit.

      Note: History of treated (ie, cured) cancer > 10 years before the Screening Visit and without recurrence can be considered based on the nature of the cancer and must be discussed with the medical monitor on a case-by-case basis.
19. Any subject who:
    a. has a diagnosis or history consistent with Antiphospholipid Syndrome (APS) (See Appendix O for APS criteria)
    b. has "triple positivity" (ie, a positive lupus anticoagulant, anticardiolipin, and anti-B2 glycoprotein). Subjects with antiphospholipid antibodies without a diagnosis of APS will be reviewed by the adjudication committee for entry into the study based on the titer, the number of positive antibodies, and other risk factors.
    c. is unwilling or unable to undergo protocol required thromboprophylaxis.
20. The subject has history of arterial or venous thrombosis.
21. The subject has a history or current diagnosis of peripheral neuropathy (sensory or motor) ≥ Grade 2 (Appendix P).
22. The subject has a presence of active uveitis or any other ophthalmological finding that in the opinion of the Investigator is clinically significant.
23. The subject has concomitant fibromyalgia, which symptoms or therapy for, in the opinion of the PI, will significantly impact the assessment of SLE disease manifestations and activity.
24. The subject has dermatomyositis, polymyositis, scleroderma, rheumatoid arthritis or other non-SLE driven inflammatory joint or skin disease or overlap syndromes as the primary disease.
25. The subject has clinically significant or unstable or uncontrolled acute or chronic disease not due to SLE (eg, cardiovascular, pulmonary, hematologic, gastrointestinal, hepatic, renal, neurological, malignancy, psychiatric or infectious disease) or laboratory abnormality or planned surgical procedure which in the opinion of the Investigator could put the subject at undue risk or confounds the ability to interpret data from the study.

Laboratory Criteria (presence of any of the following at Screening will exclude subjects from enrollment)

26. Laboratory criteria:
    - Neutrophil count < 1.5 x 10^9/L
    - White blood cell (WBC) count > 20,000/µL (> 20 X 10^9/L)
    - Lymphocyte count < 450/mm^3 (< 0.45 x 10^9/L)
    - Platelet count < 75 x 10^9/L and > 550 x 10^9/L
    - Hemoglobin < 8 g/dL or > 18 g/dL
    - Total bilirubin > 1.5 x upper limit of normal (ULN) (unless due to Gilbert's syndrome)
    - Aspartate transaminase (AST [serum glutamic oxaloacetic transaminase, SGOT]) > 2 x ULN
    - Alanine transaminase (ALT [serum glutamic pyruvic transaminase, SGPT]) > 2 x ULN

General

27. The subject is pregnant or a nursing (breast-feeding) female.
28. The subject is unlikely to comply with the study protocol or is unsuitable for any other reason, as judged by the Investigator, medical monitor or adjudication committee.
29. The subject has a history of known substance abuse within six months of the Screening Visit which, in the opinion of the Investigator, would interfere with the subject's safety or ability to comply with the study procedures. Marijuana use (whether or not medically prescribed) is not allowed within 6 weeks of Screening and during the study.
30. The subject has a history of severe allergic reactions to or hypersensitivity to any component of the IP or placebo.
31. The subject has received CC-220 in previous trials.

For Long-term Extension Phase only:

32. Subjects will not be eligible to enter the long-term extension phase if they required an increased dose of immunosuppressant medication above the maximum dose permitted in the protocol (see Section 8.1.4.1) during the last 2 months of the active treatment phase.

5. TABLE OF EVENTS

Table 3: Double-Blind Placebo-controlled Phase/Double-Blind Active Treatment Phase

Visit(s) ±1 Day (Visits 2-30)		Double-Blind Placebo-Controlled Treatment Phase[b]							Double-Blind Active Treatment Phase[b]						
	1 Screening Phase [a]	2 Baseline	3	4	5	6	7	8	9	10	11	12	13	14	15
Days	-35 to 0	0	28	56	84	112	140	168	196	224	252	280	308	336	364
Week(s)	-5 to 0	0	4	8	12	16	20	24	28	32	36	40	44	48	52
General Assessments															
Informed Consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion/Exclusion Criteria	X	X	-	-	-	-	-	-	-	-	-	-	-	-	X
Demographics	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medical/Disease History	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Prior/Concomitant Meds and Procedures	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
Efficacy Assessments															
SF-36	-	X	-	-	X	-	-	X	-	-	-	-	-	-	X
FACIT Fatigue	-	X	-	-	X	-	-	X	-	-	X	-	-	-	X
LupusPRO™	-	X	-	-	-	-	-	X	-	-	-	-	-	-	X
HAQ-DI	-	X	-	-	-	-	-	X	-	-	-	-	-	-	X
SLEDAI 2K[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SLEDAI Flare Index	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BILAG 2004	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PGA[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CLASI Activity	X	X	X	X	X	X	X	X	-	-	-	X	-	-	X

Table 3: Double-Blind Placebo-controlled Phase/Double-Blind Active Treatment Phase (Continued)

		Double-Blind Placebo-Controlled Treatment Phase[b]							Double-Blind Active Treatment Phase[b]						
Visit(s) ±1 Day (Visits 2-30)	**1 Screening Phase [a]**	**2 Baseline**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Days	**-35 to 0**	**0**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**
Week(s)	**-5 to 0**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
CLASI Damage	-	X	-	-	-	-	-	X	-	-	-	-	-	-	X
Swollen and Tender Joint Assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SLICC/ACR SLE Damage Index	-	X	-	-	-	-	-	-	-	-	-	-	-	-	X
Safety Assessments															
12-Lead ECG	X	X	X	-	-	-	-	X	X	-	-	-	-	-	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry, Hematology[e] eGFR, Urine Protein/Creatinine, and Urinalysis[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IgA,IgM,IgG	-	X	-	-	-	-	-	X	-	-	-	-	-	-	X
ESR and hs-CRP	-	X	-	-	X	-	-	X	-	-	X	-	-	-	X
Lupus Autoantibody Panel[g]	X	X	-	-	-	-	-	X	-	-	-	-	-	-	X
ds-DNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complement Panel	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lupus Antiphospholipid Profile	X	X	-	-	X	-	-	X	-	-	X	-	-	-	X
Testosterone, FSH and LH[h]	-	X	-	-	-	-	-	X	-	-	-	-	-	-	X
Pregnancy Tests[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis B and C Tests	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 3: Double-Blind Placebo-controlled Phase/Double-Blind Active Treatment Phase (Continued)

		Double-Blind Placebo-Controlled Treatment Phase[b]						Double-Blind Active Treatment Phase[b]						
Visit(s) ±1 Day (Visits 2-30)	**1 Screening Phase [a]**	**2 Baseline**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Days	**-35 to 0**	**0**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**
Week(s)	**-5 to 0**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
QuantiFERON®-TB Gold test[j]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HIV test	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Celgene Pregnancy Prevention Counseling Program (CPPCP)[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest radiograph[j]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
[redacted]															
[redacted]															
[redacted]															
[redacted]															
[redacted]															
Photographs[m]	-	X	X	X	X	X	-	X	-	-	X	-	-	-	X
Investigational Product															
Dispense IP	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X[n]
IP Accountability/Compliance	-	-	X	X	X	X	X	X	X	X	X	X	X	X	X

ANA = antinuclear antibody; BILAG = British Isles Lupus Assessment Group; CLASI = Cutaneous Lupus Area and Severity Index; ECG = Electrocardiogram; eGFR = Estimated Glomerular Filtration Rate; ESR = Erythrocyte Sedimentation Rate; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; FSH = Follicle Stimulating Hormone; HAQ-DI = Health Assessment Questionnaire-Disability Index; hs-CRP = High-Sensitivity C-Reactive Protein; IgA = Immunoglobulin A; IgG = Immunoglobulin G; IgM = Immunoglobulin M; IP = Investigational Product; LH = Luteinizing Hormone; LupusPRO = Lupus Patient Reported Outcome Tool; PD = Pharmacodynamics; PG = Pharmacogenetics: PGA = Physician's Global Assessment; PK = Pharmacokinetics; SF-36 = Short Form-36; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; SLICC/ACR SLE Damage Index = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Systemic Lupus Erythematosus Damage Index; TB = Tuberculosis.

[a] During the Screening Phase and prior to the Baseline Visit, it is recommended that sites contact subjects to evaluate their concomitant medication. This call will be used to confirm that subjects are not taking any prohibited medications and to ensure that subjects taking any protocol permitted concomitant medications are on an appropriate dose and are maintaining stable dosing according to the protocol.

[b] Subjects who discontinue the Treatment Phase early should complete the Week 104 (Visit 28) Early Termination Visit as soon as possible and enter into the Observational Follow-up Phase (Visit 29/Week 108 [males must also complete Visit 30/Week 116]).

[c] A SLEDAI 2K score and PGA must be assessed at any visit where a steroid taper is being considered or at any visit, including an unscheduled visit, where a steroid burst is being considered. For the purposes of a steroid taper or steroid burst, the "clinical" SLEDAI 2K score will be used.

[d] Height at the Screening Visit only.

[e] **Subjects taking concomitant mycophenolate mofetil, 6-mercaptopurine, mycophenolic acid, azathioprine, or calcineurin inhibitors must have hematology assessments weekly between Visit 2 (Baseline) through Visit 3 (Week 4) and Visit 8 (Week 24) through Visit 9 (Week 28). In addition, these subjects must have hematology measurements two weeks after Visit 3 [Week 4], Visit 4 [Week 8], Visit 9 [Week 28], and Visit 10 [Week 32]).**

[f] Microscopic analysis of the urine will be performed only when the dipstick is positive.

[g] This will include ANA, anti-Smith, anti-Ro, anti-LA, anti-ribonucleoprotein (RNP), and rheumatoid factor. Rheumatoid factor will be assessed at Screening (Visit 1) only.

[h] Collection of these analytes must occur at the same time of day (± 1 hour) at the Baseline (Visit 2), Week 24, and Week 52 for males only. For example, if collected at the Baseline Visit at 9 AM, the Week 24 and Week 52 sample must be collected between 8 and 10 AM.

[i] **FCBP are required to have 2 pregnancy tests during the Screening Phase. The first pregnancy test must be a serum or urine β-HCG performed within 10 to 14 days prior to the start of IP. The second test (urine) must be performed within 24 hours before starting IP. The subject may not receive IP until the Investigator has verified that the results of these pregnancy tests are negative.** See Section 6.8.6 and Table 4 for more detail.

[j] Please see Section 6.8.10 and Section 6.8.11 for greater detail on the QuantiFERON®-TB Gold test and chest radiograph.

[k] All male and FCBP subjects must be counseled about pregnancy precautions and risks of fetal exposure as described in the Pregnancy Prevention Plan. All subjects must also be counseled against sharing investigational product and donating blood during treatment with and within 28 days of discontinuing investigational product.

[l] PK blood samples will be collected prior to subjects taking their IP dose at the site on the study visit day.

[m] [redacted]

[n] For subjects who decide to enter the Observational Follow-up Phase, there will be no dispensation of IP at this visit.

Table 4: Pregnancy Testing Schedule for Females of Child Bearing Potential (FCBPs) Week 0 through Week 52

Visit(s)	Double-Blind Placebo-Controlled Treatment Phase																Double-Blinded Active Treatment Phase														
	1 SCR Phase	2 BL	LAB ONLY	LAB ONLY	LAB ONLY	3	LAB ONLY	4	LAB ONLY	5	LAB ONLY	6	LAB ONLY	7	LAB ONLY	8	LAB ONLY	LAB ONLY	LAB ONLY	9	LAB ONLY	10	LAB ONLY	11	LAB ONLY	12	LAB ONLY	13	LAB ONLY	14	LAB ONLY	15
Days	**-35 to 0**	**0**	**7**	**14**	**21**	**28**	**35**	**56**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**	**175**	**182**	**189**	**196**	**210**	**224**	**238**	**252**	**266**	**280**	**294**	**308**	**322**	**336**	**350**	**364**
Week(s)	**-5 to 0**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**25**	**26**	**27**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**
FCBPs with **regular menses**	X[a]	X	X	X	X	X	-	X	-	X	-	X	-	X	-	X	X	X	X	X	-	X	-	X	-	X	-	X	-	X	-	X
FCBPs with **irregular menses**	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

BL = Baseline; IP = investigational product; SCR = Screening.
[a] FCBPs must have a serum or urine pregnancy test within 10 to 14 days prior to the start of IP.
"LAB ONLY" indicates time points when subjects have only pregnancy testing done.

Pregnancy Testing Schedule for Females of Child Bearing Potential (FCBPs) Week 52 through Week 104

All FCBPs with reported regular menses will have pregnancy tests every 28 days throughout the Long-term Extension Phase. All FCBPs with irregular or no menses will be required to have pregnancy tests every 2 weeks throughout the Long-term Extension Phase.

Table 5: Hematology Testing Schedule for Subjects Taking Immunosuppressants (mycophenolate mofetil, 6-mercaptopurine, mycophenolic acid, azathioprine, or calcineurin inhibitors) Week 0 through Week 52

Visit(s) ±1 Day	Double-Blind Placebo-Controlled Treatment Phase													Double-Blinded Active Treatment Phase											
	1 SCR	2 BL	LAB ONLY	LAB ONLY	LAB ONLY	3	LAB ONLY	4	LAB ONLY	5	6	7	8	LAB ONLY	LAB ONLY	LAB ONLY	9	LAB ONLY	10	LAB ONLY	11	12	13	14	15
Days	**-35 to 0**	**0**	**7**	**14**	**21**	**28**	**35**	**56**	**70**	**84**	**112**	**140**	**168**	**175**	**182**	**189**	**196**	**210**	**224**	**238**	**252**	**280**	**308**	**336**	**364**
Week(s)	**-5 to 0**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**25**	**26**	**27**	**28**	**30**	**32**	**34**	**36**	**40**	**44**	**48**	**52**
Hematology testing for subjects taking immunosuppressants	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

BL = Baseline; SCR = Screening.

"LAB ONLY" indicates time points when subjects have only hematology testing done.
All subjects (regardless of background concomitant medication) will have hematology tests every 28 days from Week 52 through Week 104.

Table 6: Long-term Extension Phase

	Long-term Extension Phase													Observational Follow-up Phase	
Visit(s) ±1 Day – for all visits	**16[a]**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**Final Treatment Visit/Early Termination Visit[a] 28**	**29**	**30[h]**
Days	**392**	**420**	**448**	**476**	**504**	**532**	**560**	**588**	**616**	**644**	**672**	**700**	**728**	**756**	**812**
Week(s)	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**108**	**116**
General Assessments															
Concomitant Meds and Procedures	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	-
Efficacy Assessments															
SF-36/ FACIT Fatigue	-	-	-	-	-	X	-	-	-	-	-	-	X	X	-
HAQ-DI	-	-	-	-	-	-	-	-	-	-	-	-	X	X	-
LupusPRO™	-	-	X	-	-	X	-	-	X	-	-	-	X	X	-
SLEDAI 2K	-	-	X	-	-	X	-	-	X	-	-	-	X	X	-
SLEDAI Flare Index	-	-	X	-	-	X	-	-	X	-	-	-	X	X	-
BILAG 2004	-	-	X	-	-	X	-	-	X	-	-	-	X	X	-
PGA	-	-	X	-	-	X	-	-	X	-	-	-	X	X	-
CLASI activity	-	-	X	-	-	X	-	-	X	-	-	-	X	X	-
CLASI Damage	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-
Swollen and Tender Joint Assessments	-	-	X	-	-	X	-	-	X	-	-	-	X	X	-
SLICC/ACR SLE Damage Index	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-

Table 6: Long-term Extension Phase (Continued)

	Long-term Extension Phase													Observational Follow-up Phase	
Visit(s) ±1 Day – for all visits	**16[a]**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**Final Treatment Visit/Early Termination Visit[a] 28**	**29**	**30[h]**
Days	**392**	**420**	**448**	**476**	**504**	**532**	**560**	**588**	**616**	**644**	**672**	**700**	**728**	**756**	**812**
Week(s)	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**108**	**116**
Safety Assessments															
12-Lead ECG[g]	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-
Vital Signs	-	-	X	-	-	X	-	-	X	-	-	-	X	X	-
Physical Exam	-	-	X	-	-	X	-	-	X	-	-	-	X	X	-
Chemistry, Urinalysis, eGFR Urine Protein/Creatinine	-	-	X	-	-	X	-	-	X	-	-	-	X	X	-
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
IgA,IgM,IgG	-	-	-	-	-	X	-	-	-	-	-	-	X	-	-
ESR and hs-CRP	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-
Lupus Autoantibody Panel[c]	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-
ds-DNA	-	-	X	-	-	X	-	-	X	-	-	-	X	X	-
Complement Panel	-	-	X	-	-	X	-	-	X	-	-	-	X	X	-
Lupus Antiphospholipid Profile	-	-	X	-	-	X	-	-	X	-	-	-	X	-	-
Testosterone, FSH and LH[b]	-	-	-	-	-	X	-	-	-	-	-	-	X	-	X
Pregnancy Test[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
QuantiFERON®-TB Gold test[e]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Celgene Pregnancy Prevention Counseling Program (CPPCP)[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-

Table 6: Long-term Extension Phase (Continued)

	Long-term Extension Phase													Observational Follow-up Phase	
Visit(s) ±1 Day – for all visits	**16[a]**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**Final Treatment Visit/Early Termination Visit[a] 28**	**29**	**30[h]**
Days	**392**	**420**	**448**	**476**	**504**	**532**	**560**	**588**	**616**	**644**	**672**	**700**	**728**	**756**	**812**
Week(s)	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**108**	**116**
Investigational Product															
Dispense IP	X	X	X	X	X	X	X	X	X	X	X	X	-	-	-
IP Accountability/Compliance	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-

ANA = antinuclear antibodies; BILAG = British Isles Lupus Assessment Group; CLASI = Cutaneous Lupus Area and Severity Index; ECG = Electrocardiogram; eGFR = Estimated Glomerular Filtration Rate; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; FCBP = female of child bearing potential; FSH = Follicle Stimulating Hormone; HAQ-DI = Health Assessment Questionnaire-Disability Index; IgA = Immunoglobulin A; IgG = Immunoglobulin G; IgM = Immunoglobulin M; IP = Investigational Product; LH = Luteinizing Hormone; LupusPRO = Lupus Patient Reported Outcome Tool; PGA = Physician's Global Assessment; SF-36 = Short Form-36; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; SLICC/ACR SLE Damage Index = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Systemic Lupus; Erythematosus Damage Index; TB = tuberculosis.

[a] Subjects who discontinue from the study during the Long-term Extension Phase should complete the Week 104 (Visit 28) Early Termination Visit as soon as possible and enter into the Observational Follow-up Phase (Visit 29/Week 108 [males must also complete Visit 30/Week 116]).

[b] Collection of these analytes must occur at the same time of day (± 1 hour) at Week 76, Week 104 (End of Treatment or Early Termination Visit), and Week 116 for males only. For example, if collected at the Week 64 at 9 AM, the Week 76, Week 88, Week 104, and Week 116 sample must be collected between 8 and 10 AM.

[c] This will include ANA, anti-Smith, anti-Ro, anti-LA, and anti-ribonucleoprotein (RNP).

[d] **FCBP may not receive IP until the Investigator has verified that the subject's urine pregnancy test results are negative. Serum pregnancy tests may be performed as needed. FCBP with reported regular cycles must have pregnancy testing every 28 days during the Long-term Extension Phase, at study discontinuation and at 28 days after the last dose of IP. If menstrual cycles are irregular, pregnancy testing must occur every 14 days while on IP, at study discontinuation and at 14 and 28 days following study discontinuation.**

[e] Please see Section 6.8.10 for greater detail on the QuantiFERON®-TB Gold test.

[f] All male and FCBP subjects must be counseled about pregnancy precautions and risks of fetal exposure as described in the Pregnancy Prevention Plan. All subjects must also be counseled against sharing investigational product and donating blood during treatment with and within 28 days of discontinuing investigational product.

[g] ECGs may be performed at any time during the Long-term Extension Phase if clinically warranted.

[h] Visit 30 is only for males to collect male hormones (LH, FSH, and testosterone).

6. PROCEDURES

Signed informed consent forms (ICFs) must be obtained before any study evaluations or procedures are performed and any samples are collected per local regulations during the course of the study.

Waivers to the protocol will not be granted during the conduct of this trial.

Any questions regarding the protocol should be directed to the Medical Monitor or designee.

6.1. Screening Phase

Screening evaluations will be performed for all subjects to determine eligibility. These evaluations should be completed within 5 weeks of Baseline (Visit 2). In the event that the subject will exceed the 5-week Screening Phase the medical monitor must be contacted.

Subjects are permitted to be re-screened two times should they fail to meet the study entry criteria. Note: Subjects who fail entry criteria due to a positive hepatitis B, hepatitis C, HIV or TB test result should not be rescreened for the study.

Safety laboratory analyses will be performed by the contracted central laboratory. The central laboratory will provide a separate manual for the collection and processing of the samples for this study. Screening laboratory values must demonstrate subject eligibility, but may be repeated once within the Screening Phase, if necessary.

During the Screening Phase and prior to the Baseline Visit, it is recommended that sites contact subjects to evaluate their concomitant medication. This call will be used to confirm that subjects are not taking any prohibited medications and to ensure that subjects taking any protocol permitted concomitant medications are on an appropriate dose and are maintaining stable dosing according to the protocol. The Screening Visit should be registered using IRT.

The following order of procedures should be considered after informed consent has been obtained:

- Inclusion/exclusion criteria eligibility (see Section 4.2 and Section 4.3)
- Demographics (initials, date of birth, sex, race, ethnicity [if allowed by local regulations])
- Disease history including specific information regarding SLE
- Complete medical history (all relevant medical conditions diagnosed and those occurring prior to Screening)
- Prior and concomitant medication evaluation (including any non-SLE medications taken within one month prior to Screening)
- Prior and concomitant SLE medication evaluation (previous use of antimalarial, immunosuppressant, biologic or other medication relevant to the SLE management should be recorded, regardless of when it was administered. For steroids, a reporting period of 3 months for orals and 6 months for IV or IM preparations prior to Screening is sufficient.)
- Prior procedures evaluation
- Vital signs, weight, and height (see Section 6.8.2)
- Physical examination (see Section 6.8.3)

- Standard 12-lead ECGs (see Section 6.8.4)
- The following laboratory assessments (Section 6.8.5) will be collected:
  - Hematology panel
  - Chemistry panel
  - Urinalysis
  - Lupus antiphospholipid profile
  - Lupus autoantibody panel
  - ds-DNA
  - Complement panel
- Pregnancy test (a serum or urine β-HCG must be performed within 10 to 14 days prior to the start of IP and a second pregnancy test [urine] must be performed within 24 hours before starting IP) (see Section 6.8.6)
- Hepatitis B and C testing (Section 6.8.8)
- HIV test (Section 6.8.9)
- QuantiFERON®-TB Gold (see Section 6.8.10)
- Counseling about pregnancy precautions and the potential risks of fetal exposure (see Section 6.8.7)
- Efficacy assessments (see Section 6.9 for the recommended order).
- Adverse event assessment (begins when the subject signs the informed consent and is assessed continuously throughout the study until 28 days following cessation of IP) (see Section 6.8.1)
- Chest radiograph (see Section 6.8.11) (A chest radiograph should be taken prior to the Baseline Visit, when most of the eligibility criteria are met, so that results are available prior to Baseline Visit).

All clinically significant abnormal ECG, laboratory and physical exam findings identified during the Screening Phase will be captured on the medical history page of the electronic case report form (eCRF). Refer to Section 10 for details pertaining to AEs. Adverse event assessment begins when the subject signs the informed consent form. If a subject is hospitalized for a serious adverse event, additional information will be collected regarding reason and duration of hospitalization and to which unit the subject was admitted.

At a minimum the informed consent date, demographics, and reason why the subject did not qualify for the study will be collected for all subjects determined to be screen failures. Adverse events experienced by screen failure subjects will be collected from the date of signing consent to the day the subject is confirmed to be a screen failure. This information will be captured in the subject's source documents and appropriate CRF(s).

For purposes of study eligibility, inclusion and exclusion criteria/results should be reviewed again prior to randomization (Baseline [Visit 2]) to ensure the subject continues to meet criteria for entry into the study (Section 4.2 and Section 4.3). Subjects eligibility for enrollment will be adjudicated during the Screening Phase and prior to Randomization.

6.2. Treatment Phase

The subject will begin treatment upon confirmation of eligibility by the adjudication committee. Investigational product is provided as a 28-day supply. Therefore, only a ± 1-day window for all study visits is allowed.

On study visit days, pregnancy testing should be done prior to taking IP.

At Weeks 4, 12, and 24 subjects must take their IP at the study site after PK samples have been collected.

Site personnel responsible for conducting efficacy assessments are not permitted to see subjects' completed QOL questionnaires.

The following order of procedures should be considered:

- Pregnancy test (urine or serum) (see Section 6.8.6)
- Pharmacokinetic testing (see Section 6.10)
- Adverse event assessment (see Section 6.8.1)
- Disease history including specific information regarding SLE
- Concomitant procedures and medications
- Quality-of-life assessments (see Section 6.9)
- Physical examination (see Section 6.8.3)
- Vital signs and weight (see Section 6.8.2)
- Efficacy assessments (see Section 6.9)
- The following laboratory assessments (Section 6.8.5) will be collected:
  - Hematology panel
    - Subjects taking concomitant mycophenolate mofetil, 6-mercaptopurine, mycophenolic acid, azathioprine, or calcineurin inhibitors must have weekly hematology assessments between Visit 2 [Baseline] through Visit 3 [Week 4] and Visit 8 [Week 24] through Visit 9 [Week 28]. In addition, these subjects must have hematology measurements two weeks after Visit 3 [Week 4], Visit 4 [Week 8], Visit 9 [Week 28], and Visit 10 [Week 32]).
  - Chemistry panel
  - Complement panel
  - Testosterone, FSH and LH
  - Lupus autoantibody panel
  - ds-DNA
  - Immunoglobulin assessment
  - Erythrocyte sedimentation rate (ESR) and high-sensitivity c-reactive protein (hs-CRP)
  - Lupus antiphospholipid profile
- Pharmacodynamic and pharmacogenetic testing (see Section 6.11)
- Urinalysis
- Counseling about pregnancy precautions and the potential risks of fetal exposure (see Section 6.8.7)
- Standard 12-lead ECGs (see Section 6.8.4)

- IP compliance assessment (all used and unused blister cards must be returned at every visit)
- Dispensation of IP
- Photography (only for subjects at selected sites in the US)

6.3. Long-term Extension Phase

Participation in the Long-term Extension Phase is optional. Subjects who elect not to continue in the Long-term Extension Phase at the completion of the Blinded Active Treatment Phase, should enter the Observational Follow-up Phase as detailed in Section 6.5. In order to enter the Long-term Extension Phase subjects must meet entry criteria specified for the Long-term Extension Phase in Section 4.2 and Section 4.3. For all Long-term Extension Phase visits, IP is provided as a 28-day supply. Therefore only ± 1-day window for all visits is allowed.

On study visit days, pregnancy testing should be done prior to taking IP.

Worsening of a subject's SLE should be considered as worsening of the disease under study, and should not be captured as an adverse event unless it meets the criterion of a SAE.

Site personnel responsible for conducting efficacy assessments are not permitted to see subjects' completed QOL questionnaires.

The following order of procedures should be considered:

- Pregnancy test (urine or serum) (see Section 6.8.6)
- Adverse event assessment (see Section 6.8.1)
- Concomitant procedures and medications
- Quality-of-life assessments (see Section 6.9)
- Physical examination (see Section 6.8.3)
- Vital signs and weight (see Section 6.8.2)
- Efficacy assessments (see Section 6.9)
- The following laboratory assessments (Section 6.8.5) will be collected:
  - Hematology panel
  - Chemistry panel
  - Complement panel
  - Testosterone, FSH and LH
  - Lupus autoantibody panel
  - ds-DNA
  - Immunoglobulin assessment
  - Lupus antiphospholipid profile
- Urinalysis
- QuantiFERON®-TB Gold (see Section 6.8.10)
- Counseling about pregnancy precautions and the potential risks of fetal exposure (see Section 6.8.7)
- Standard 12-lead ECGs (see Section 6.8.4).
- IP compliance assessment (all used and unused medication containers must be returned at every visit)
- Dispensation of IP

6.4. End of Treatment/Early Termination

An early termination visit will be performed for subjects who are withdrawn from treatment for any reason as soon as possible after the decision to permanently discontinue treatment has been made.

The following order of procedures should be considered:

- Pregnancy test (urine or serum) (see Section 6.8.6)
- Adverse event assessment
- Concomitant procedures and medications
- Quality-of-life assessments (see Section 6.9)
- Physical examination
- Vital signs
- Efficacy assessments (see Section 6.9)
- The following laboratory assessments (Section 6.8.5) will be collected:
  - Hematology panel
  - Chemistry panel
  - Complement panel
  - Testosterone, FSH and LH
  - Lupus autoantibody panel
  - ds-DNA
  - Immunoglobulin assessment
  - Lupus antiphospholipid profile
- Urinalysis
- Counseling about pregnancy precautions and the potential risks of fetal exposure (see Section 6.8.7)
- Standard 12-lead ECGs
- IP compliance assessment (all used and unused blister cards must be returned at every visit)

6.6. Unscheduled Visit for SLE Flare

Subjects experiencing SLE flares must meet steroid burst criteria (Section 8.1.2) in order to receive a steroid burst. In the event a SLE flare requiring an increase in steroids occurs outside of a protocol specified visit, subjects should come to the site for an unscheduled visit in order to qualify for a steroid burst.

The following evaluations will be performed as specified:

- Adverse event assessment (see Section 6.8.1)
- Concomitant procedures and medications (Section 6.7.4)
- The following laboratory assessments (Section 6.8.5) will be collected:
  - Hematology panel
  - Chemistry panel
  - ds-DNA
  - Complement panel
  - Urinalysis
- SLEDAI2K, BILAG, and PGA (see Section 6.9).

6.7. General Assessments

6.7.1. Informed Consent

Informed consent must be obtained by the Investigator or designee for all subjects prior to the initiation of any study procedures. All subjects must review the ICF prior to the initiation of any study procedures and indicate whether or not they consent to participate in this portion of the study.

6.7.2. Inclusion/Exclusion Criteria

Subjects must meet all inclusion criteria (Section 4.2) and must not have any of the conditions specified in the exclusion criteria (Section 4.3). The subjects' source documents must support his/her qualifications for the study (eg, for females not of childbearing potential [FNCBP] who do not require pregnancy testing or birth control because of hysterectomy, the date of the hysterectomy must be included in the medical history [Section 6.8.6]).

6.7.3. Complete Medical and Disease History

Medical history should be recorded, including previous surgeries. History of SLE will be reported in a disease-specific electronic case report form (eCRF) including diagnosis date and date of skin and joint manifestations (if applicable).

6.7.4. Prior and Concomitant Medications

Information regarding prior/concomitant medication usage will be collected for each subject. All medications and therapies (including systemic and topical medications, prescription, and non-prescription, including herbal supplements) taken by the subject up to 30 days prior to Visit 1 should be recorded, including the stop dates for medications prohibited in the study, at the time of consent.

Previous use of antimalarial, immunosuppressant, biologic or other medication relevant to the SLE management should be recorded, regardless of when they were administered. For steroids, reporting period of 3 months for orals and 6 months for IV or IM preparations prior to Screening Visit is sufficient.

At the Screening and Baseline Visits, concomitant medications should be checked against the list of prohibited medications to ensure the protocol requirements have been met. Refer to Protocol Section 8.1 for permitted and Section 8.2 for prohibited medications. If a subject does not meet the medication requirements, the study visit must be rescheduled.

6.8. Safety Assessments

The following assessments will be performed as outlined in Section 5.

6.8.1. Adverse Event Assessment

Adverse event assessment begins when the subject signs the informed consent form (see Section 10.1 for information on definition and attribution of AEs). Information regarding all AEs regardless of causal relationship to IP (CC-220 or placebo) will be collected. The time frames for recording all AEs are indicated in Section 5. Worsening of a subject's SLE or SLE flares should be considered as worsening of the disease under study and not recorded as an AE unless the event meets the definition of a SAE.

6.8.2. Vital Signs

Vital signs include temperature, pulse, and seated blood pressure. Blood pressure will be measured after the subject has been seated and resting quietly for 5 minutes. If body temperature is measured orally, since drinking hot or cold beverages (including water) has a significant impact on recorded oral body temperature, no beverages should be ingested within 15 minutes of the measurement. Investigators are to report any clinical significant abnormal findings as AEs.

6.8.3. Physical Examination

Physical examinations will include height (Screening only) and weight (to be done in street clothes, no shoes), mucocutaneous, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal system evaluations. Physical examinations should also be guided by the subject's symptomology. Results of the physical examinations will be recorded only in the source documents. Clinically significant abnormal findings identified during the Screening physical examination will be recorded on the eCRF as medical history. Gynecological and urogenital examinations will not be done unless for cause. The frequency of these assessments is detailed in Section 5.

6.8.4. Standard 12-lead ECGs

All ECGs will be performed after the subject has been in the supine position for 3 minutes. All ECG recordings will be manually over-read on an ongoing basis by a cardiologist at the core ECG laboratory for QT measurement and QTc calculation using Fridericia's formula (QTcF). The central cardiologist will interpret all ECGs with respect to PR interval, QRS duration, heart rate and R-R interval, QT and QTcF intervals and for arrhythmia, ischemia or any relevant finding. Details regarding the ECG recordings are described in a separate manual.

6.8.5. Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed as indicated in Section 5.

A central laboratory will be used for this study. The Principal Investigator or medically-qualified designee will review and assess all clinical laboratory results for each subject participating at their sites, and indicate whether the results are clinically significant. Repeat clinical safety laboratory evaluations should be performed if judged clinically appropriate by the PI or by a medically-qualified designee. The laboratory reports should be initialled and dated by the Investigator or medically-qualified designee to indicate that they have been reviewed. Any clinically significant abnormal laboratory result that is not part of the disease under study should be reported as a separate AE and should be followed to resolution (eg, stabilizes, returns to baseline, or improves and considered as no longer clinically significant).

Clinical laboratory evaluations will include:

Category	Parameters
Hematology[a]	Complete Blood Count (CBC): hematocrit, hemoglobin, platelets, red blood cell count (RBC), and white blood cell count (WBC) with differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils [percent and absolute count])
Serum Chemistry	Albumin, alanine aminotransferase (ALT; serum glutamic pyruvic transaminase [SGPT]), alkaline phosphatase, aspartate aminotransferase (AST; serum glutamic oxaloacetic transaminase [SGOT]), bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, creatinine kinase, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total bilirubin, direct bilirubin, indirect bilirubin, total cholesterol, total protein, triglycerides, lipase, and amylase
Dipstick Urinalysis[b]	Color, bilirubin, blood, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, and urobilinogen
Microscopic Urinalysis	RBCs, WBCs, casts, crystals, bacteria, and epithelial cells
[redacted]	[redacted]
Immunoglobulins	IgG, IgM, and IgA
Hormones	Testosterone, FSH, and LH Collection of these analytes must occur at the same time of day (± 1 hour) for males only. For example, if collected at the Baseline Visit at 9 AM, subsequent samples must be collected between 8 and 10 AM.

Category	Parameters
Hepatitis	Hepatitis B and C Serological tests for hepatitis B and C will be performed at the Screening Visit.
HIV	Serological tests for HIV-1 and HIV-2 will be performed at the Screening Visit.
Inflammation	ESR and hs-CRP
Lupus autoantibodies	ANA, anti-dsDNA[c], anti-Smith, anti-Ro, anti-LA, anti-ribonucleoprotein (RNP), and rheumatoid factor[d]
Complement Panel	C3, C4, and CH50
Lupus antiphospholipid profile	Lupus anticoagulant, anti-cardiolipin antibodies, and beta-2–glycoprotein I antibodies

[a] Subjects taking concomitant mycophenolate mofetil, 6-mercaptopurine, mycophenolic acid, azathioprine, or calcineurin inhibitors must have weekly hematology assessments between Visit 2 [Baseline] through Visit 3 [Week 4] and Visit 8 [Week 24] through Visit 9 [Week 28]. In addition, these subjects must have hematology measurements two weeks after Visit 3 [Week 4], Visit 4 [Week 8], Visit 9 [Week 28], and Visit 10 [Week 32]).
[b] Use clean catch technique for urine sample.
[c] Anti-dsDNA will be collected at every visit in the Placebo-Controlled and Active Treatment Phase while ANA, anti-Smith, anti-Ro, anti-LA, and anti-ribonucleoprotein will be collected at Visits 1, 2, 8, and 15. In the Long-Term Extension Phase, anti-dsDNA will be collected at Visits 18, 21, 24, 28, and in the Observational Follow-up Phase at Visit 29 while ANA, anti-Smith, anti-Ro, anti-LA, and anti-ribonucleoprotein will be collected at Visit 28.
[d] Rheumatoid factor will be assessed only at Screening (Visit 1).

6.8.6. Pregnancy Test

A pregnancy test (urine or serum) is required for all female subjects of childbearing potential throughout the study as specified in Section 5. All FCBP are required to have 2 negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting IP. **A serum or urine β-HCG pregnancy test must be performed within 10 to 14 days prior to the start of IP and a second pregnancy test (urine) must be performed within 24 hours before starting IP. The subject may not receive IP until the Investigator has verified that the results of these pregnancy tests are negative.**

FCBP with reported regular cycles must have pregnancy testing weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at Visit 29 (Week 108) following IP discontinuation (if urine pregnancy test is positive at Visit 29 (Week 108), a serum pregnancy test must be conducted to confirm result). Weekly pregnancy tests must be obtained between Visit 2 (Baseline) through Visit 3 (Week 4) and Visit 8 (Week 24) through Visit 9 (Week 28). The physician in concert with the subject should determine whether the subject has irregular menses. For those FCBP with menstrual cycles that are irregular, pregnancy testing must occur weekly (as described above) and then every 14 days while on study, at study discontinuation and at 14 and 28 days following study discontinuation. At every visit, the Investigator must verify that the results of these pregnancy tests are negative prior to providing the subject with IP.

Females who are not of childbearing potential (FNCBP) and do not require pregnancy testing or birth control must provide sufficient evidence such as, but not limited to, history of

hysterectomy, bilateral oophorectomy, and/or being postmenopausal for at least 24 consecutive months (that is, has not had menses at any time during the preceding 24 consecutive months).

6.8.7. Pregnancy Prevention and Counseling

Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted for all subjects as described in the Pregnancy Prevention Plan (provided separately).

Females of childbearing potential enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg, calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting CC-220; 2) while taking CC-220; 3) during dose interruptions; and 4) for at least 28 days after the last dose of CC-220.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. If the below contraception methods are not appropriate for the FCBP, she must be referred to a qualified provider of contraception methods to determine the medically effective contraception method appropriate to the subject. The following are examples of highly effective and additional effective methods of contraception:

Examples of highly effective methods:

- Intrauterine device (IUD)
- Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [eg, desogestrel]). Estrogen-free formulations are recommended.
- Tubal ligation
- Partner's vasectomy

Examples of additional effective methods:

- Male condom
- Diaphragm
- Cervical Cap

Male subjects must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg, calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking CC-220, during dose interruptions and for at least 90 days following the last dose of CC-220, even if he has undergone a successful vasectomy.

6.8.8. Hepatitis B and C

Hepatitis B and hepatitis C testing will be performed at Screening. The hepatitis screen includes testing for hepatitis B surface antigen and antibody, hepatitis B core antibodies (IgG/IgM), and

antibodies to hepatitis C. The Investigator should refer the subject to his/her general practitioner or other appropriate healthcare provider for further follow-up, if testing is positive.

6.8.9. Human Immunodeficiency Virus

The HIV testing will be performed at Screening unless prohibited by local health authority guidelines. The HIV test uses an antigen/antibody combination immunoassay that detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen to screen for established infection with HIV-1 or HIV-2 and for acute HIV-1 infection. The Investigator should refer the subject to his/her general practitioner or other appropriate healthcare provider for further follow-up and counseling (per the Investigator's medical practice procedure and local guidelines), if testing is positive.

6.8.10. QuantiFERON-TB

All subjects will be required to have a QuantiFERON-TB Gold at their Screening Visit to ensure they do not have active or latent mycobacterium tuberculosis infection. This test is an Interferon-Gamma Release Assay which uses whole-blood to help diagnose *Mycobacterium tuberculosis* infection. Subjects with a QuantiFERON-TB Gold test result at Screening elevated to above normal as per the central laboratory will not be permitted to enter the study.

6.8.11. Chest Radiograph

Subjects must have a normal chest radiograph. Results must be within normal limits or not clinically significant in order to allow a subject to enroll in the study. A chest radiograph should be taken prior to the Baseline Visit, when most of the eligibility criteria are met, so that results are available prior to the Baseline Visit. A posterior-anterior (PA) radiograph is required. A lateral view is strongly recommended unless prohibited by local health authority requirements. Alternatively, PA or PA/lateral radiographs or chest CT scans that were taken within the 3 months (or longer periods based on local health authority requirements) prior to the Screening Visit will be accepted for evaluation for participation in the study. Additional chest radiographs should be performed as indicated by local health authorities or treatment guidelines. Chest radiographs should be performed when clinically indicated. If the screening chest radiograph is indeterminate, please contact the medical monitor to discuss.

Note: If screening chest radiograph shows abnormalities with no significant changes from previous radiographs, then the subject may be considered for enrollment. Please contact the medical monitor to discuss prior to entry.

6.9. Clinical Efficacy Assessments

Efficacy assessments should be conducted by the same qualified person throughout the study. Cutaneous Lupus Area and Severity Index (CLASI), Swollen and Tender Joint Counts, SLEDAI 2K, SLICC/ACR SLE Damage Index, PGA and BILAG 2004 assessments must be conducted by a physician, physician assistant, or qualified nurse practitioner. Efficacy assessments should be conducted by the same qualified person throughout the study. The CLASI, SLEDAI 2K, and BILAG 2004 assessments must be performed by a physician, physician assistant, or qualified nurse practitioner who has been certified through the online instrument training specific to the study. Any qualified personnel who has a valid certification through the LFA website will not be required to re-certify.

It is recommended that health assessment questionnaires be completed prior to any other study activities so that responses most accurately reflect subjects' experiences before the study visit. If the subject needs help in completing the questionnaires, assistance should only be provided by study staff and not by family members.

6.9.1. Functional Assessment of Chronic Illness Therapy (FACIT) – Fatigue Scale

The FACIT-Fatigue scale (Yellin, 1997; Appendix H) is a 13-item self-administered questionnaire that assesses both the physical and functional consequences of fatigue. Each question is answered on a 5-point scale, where 0 means "not at all," and 4 means "very much." The total FACIT-Fatigue score ranges from 0 to 52.

6.9.3. LupusPRO™

The LupusPRO™ (Appendix K) is a disease targeted patient reported outcome tool for patients with SLE. It was developed from ethnically diverse US patients with SLE. It has been validated for use in the US. It has 49 items of which 30 items are for health related quality of life. The instrument has a 6 point Likert response format, where 0=None of the time, 1= A little of the time, 2= Some of the time, 3=Most of the time, 4= All of the time, and 5= Not applicable. Scores for this tool range from 0 (worst QoL) to 100 (best QoL) (Jolly, 2008; Cervera, 2009).

6.9.4. HAQ-DI

The HAQ-DI (Appendix L; Fries, 1980) is a 20-question, self-administered instrument that measures the subject's functional ability on a 4-level difficulty scale (0 to 3, with 0 representing

normal or no difficulty; and 3 representing an inability to perform). Eight categories of functioning are included: dressing, rising, eating, walking, hygiene, reach, grip, and usual activities (Bruce, 2003). This scale is sensitive to change and is a good predictor of future disability (Aletaha, 2006).

6.9.5. SLEDAI 2K

The SLEDAI 2K score (Appendix B; Gladman, 2002) measures disease activity through assessment of 24 lupus manifestations using a weighted score of 1 to 8 points. A manifestation is recorded if it is present over the previous 30 days regardless of severity or whether it has improved or worsened. A SLEDAI 2K score of 3 to 4 points is representative of active disease and a decrease of 1 to 2 points is considered clinically meaningful. In addition to capturing changes in disease activity, the SLEDAI 2K captures the occurrence of SLE flares using the SLE Flare Index. The SLE Flare Index is defined by an increase in the SLEDAI of 3 or more points (mild or moderate flare) or a SLEDAI score greater than 12 (severe), a 0 to 3 visual analogue scale (VAS) with anchors for the physician global assessment (none, mild, moderate or severe flare) with an increase in 1 (for mild/moderate) or 2.5 (for severe) and adding NSAIDs or hydroxychloroquine (for mild) or steroids, but no more than 0.5 mg/kg/day and/or adding a new immunosuppressant (for severe) (Pope, 2014).

6.9.6. SLE Flare

The occurrence of SLE flares will be captured by the SLEDAI 2K, BILAG, and PGA. Subjects experiencing SLE flares should come to the site for an unscheduled visit. All flares will be adjudicated by reviewing the SLEDAI Flare index and BILAG in a blinded fashion for severity (mild, moderate, severe).

6.9.7. British Isles Lupus Assessment Group 2004 (BILAG)

The BILAG 2004 (Isenberg, 2005; Appendix C) is a composite index that is based on the Classic BILAG index. It is a clinical measure of lupus disease activity. This tool assesses the changing severity of clinical manifestations of SLE using an ordinal scale scoring system that contain 9 systems (constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, gastrointestinal, ophthalmic, renal and hematological). Activity in each organ system is scored as: A=most active disease; B=intermediate activity; C=mild, stable disease; D=previous involvement, currently inactive; E=no previous activity.

6.9.8. Physician's Global Assessment (PGA)

The PGA (Appendix G; Furie, 2009) uses a visual analog scale with scores between 0 and 3 to indicate worsening of disease. The scoring is as follows:

- 0 = none
- 1 = mild disease
- 2 = moderate disease
- 3 = severe disease

6.9.9. CLASI Activity Score Assessment

The CLASI Activity Score (Appendix D; Albrecht, 2005) ranges from 0 to 70. To generate the activity score erythema is scored on a scale of 0 (absent) to 3 (dark red; purple/violaceous/crusted/hemorrhagic) and scale/hypertrophy are scored on a scale of 0 (absent) to 2 (verrucous/hypertrophic). Both the erythema and scale/hypertrophy scores are assessed in 13 different anatomical locations. In addition, the presence of mucous membrane lesions is scored on a scale of 0 (absent) to 1 (lesion or ulceration), the occurrence of recent hair loss is captured (1=yes; 0=no) and non-scarring alopecia is scored on a scale of 0 (absent) to 3 (focal or patchy in more than one quadrant). To calculate the activity score, all scores for erythema, scale/hypertrophy, mucous membrane lesions and alopecia are added together.

6.9.10. CLASI Damage Score Assessment

The CLASI Damage Score (Appendix D; Albrecht, 2005) ranges from 0 to 56. To generate the damage score, dyspigmentation is scored on a scale of 0 (absent) to 1 (dyspigmentation) and scarring/atrophy/panniculitis are scored on a scale of 0 (absent) to 2 (severely atrophic scarring or panniculitis). Both the dyspigmentation and scarring/atrophy/panniculitis scores are assessed as usually lasting greater than or less than 12 months for the subject. If the dyspigmentation usually lasts greater than 12 months, the dyspigmentation scoring conducted for the 13 anatomical areas is doubled. In addition, scarring of the scalp (judged clinically), is scored on a scale of 0 (absent) to 6 (affects the whole skull). To calculate the damage score, all scores for dyspigmentation, scarring/atrophy/panniculitis, and scarring of the scalp are added together.

6.9.11. Swollen and Tender Joint Count

Joint tenderness and swelling will be noted as “present” or “absent,” with no quantitation of severity. The 28 assessed joints are illustrated in Appendix F. In order to maintain consistency throughout the study, the same evaluator should perform the joint assessments for a given subject at a study site at each study visit.

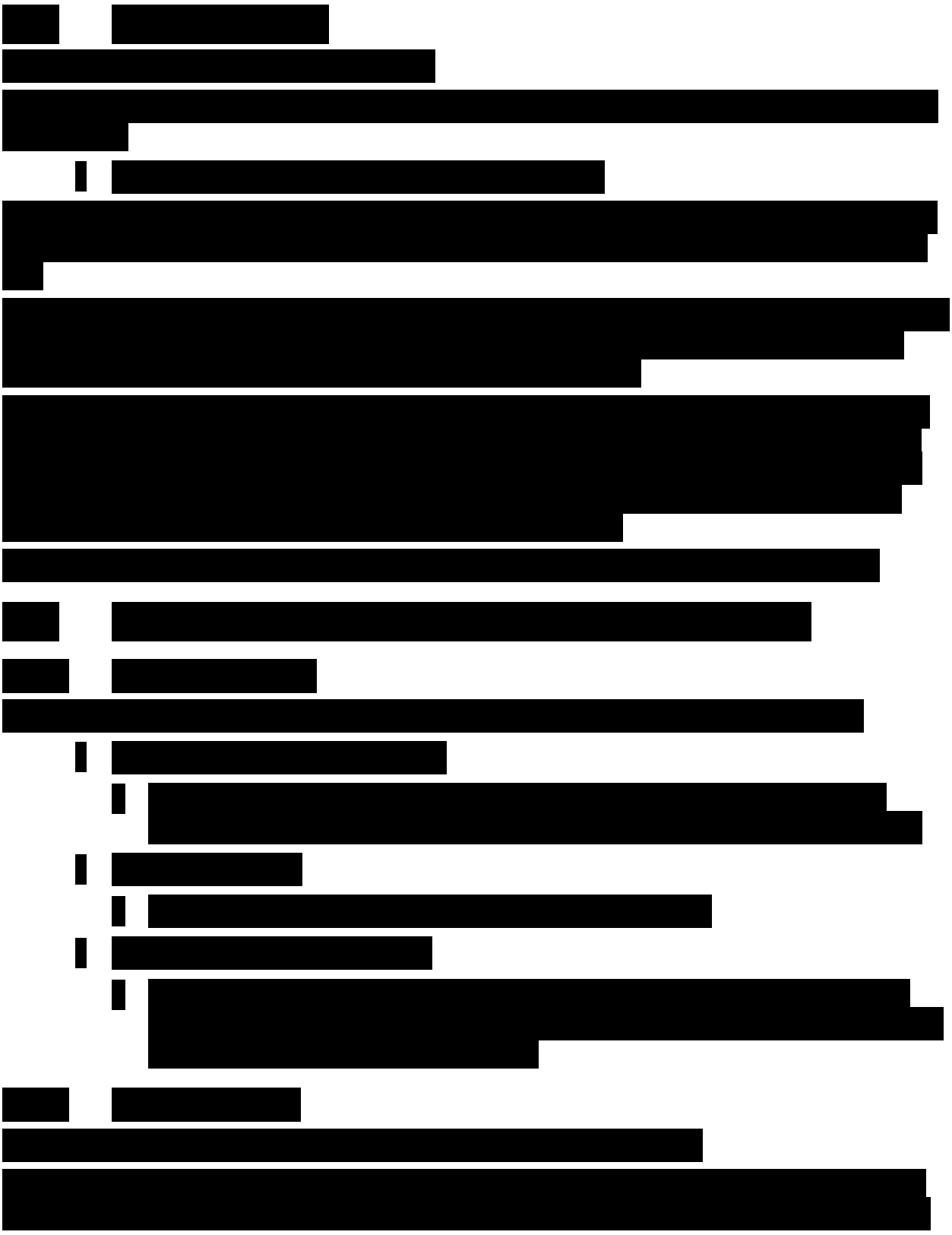
6.9.12. SLICC/ACR SLE Damage Index

The SLICC/ACR Damage Index (Appendix M; Stoll, 2004) measures irreversible impairment since onset of SLE which has to be present for at least 6 months. Damage is defined for 12 separate organ systems: ocular (range 0-2), neuropsychiatric (0-6), renal (0-3), pulmonary (0-5), cardiovascular (0-6), peripheral vascular (0-5), gastrointestinal (0-6), musculoskeletal (0-7), skin (0-3), endocrine (diabetes) (0-1), gonadal (0-1) and malignancies (0-2). The maximum score for this assessment is 47 points.

6.9.13. Photography

Photographic assessments may be done at selected sites in the United States to provide supportive evidence of efficacy as scheduled in Table 3. In order to be eligible for photography, subjects must have a CLASI activity score of at least 10 at Screening. Subjects with no Baseline photographs should not have subsequent photographs taken. The procedure for taking the photographs and processing photographs will be described in a separate procedure manual distributed to investigational sites performing photographic assessments. Photographic

assessments are an optional part of this study. Subjects enrolled at the selected photography sites will be asked to provide separate consent prior to being photographed.



7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product(s)

CC-220 has a chemical structure of 2,6-piperidinedione, 3-[1,3-dihydro-4-[[4-(4-morpholinylmethyl)phenyl]methoxy]-1-oxo-2H-isoindol-2-yl]-, (3S)-, hydrochloride (1:1). It has a molecular weight of 485.96 g/mol.

CC-220 will be provided by the sponsor as 0.15 mg (size #4), 0.3 mg (size #4), and 0.45 mg (size #3) formulated capsules (equivalent to 0.162 mg, 0.324 mg, and 0.486 mg hydrochloric acid salt, respectively) and will be labeled appropriately as investigational material. Excipients of the formulated capsules include anhydrous lactose, pregelatinized starch, stearic acid and gelatin capsules.

In addition, the sponsor will provide size #4 matching placebo identical in appearance to CC-220 0.15 mg, and 0.3 mg, and size #3 matching placebo identical in appearance to CC-220 0.45 mg formulated capsules labeled appropriately as investigational material.

Each daily dose will consist of one size #3 capsule (either placebo or 0.45 mg) and one size #4 capsule (either placebo or 0.15 mg or 0.3 mg) depending on the assigned treatment.

7.2. Treatment Administration and Schedule

Investigational product will be taken orally once daily without respect to food or drink at approximately the same time every day in the morning.

To maintain the blind at the site and subject level, the original individual subject treatment assignments at randomization will not be revealed to the Investigators until after the 52 Week database lock and after all final analyses are completed and the final results have been released.

Capsules of CC-220 will be counted at every visit starting at Visit 3 through the completion of the study. If a dose of IP is missed for the entire day, the subject should not take an extra dose the next day or take an unscheduled dose. Subjects who take more than the prescribed dose of IP should be instructed to contact study staff immediately and seek emergency medical care if needed.

Any interruption in the IP will not alter the current dose or dose interval, nor will the length of the study be extended to account for days of missed IP.

The sponsor asks to be notified in advance of planned IP dosage interruptions or modifications; however, the decision to modify IP dosing will be based on the Investigator's clinical judgment.

7.2.1. Overdose

Overdose, as defined for this protocol, applies to protocol-required dosing of the IP (CC-220) only. Therefore, for a drug to be subject to the overdose definition it must be both required and an IP. In this study the only required IP is CC-220 and placebo, hence the overdose definition will apply to only CC-220 (or matching placebo). Other required or optional non-IP intended for prophylaxis of certain side effects, to treat the disease, etc, are excluded from this definition.

On a per dose basis, an overdose is defined as any amount over the protocol-specified dose of CC-220 given to a subject, regardless of any associated adverse events or sequelae.

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

The reporting cutoff was intentionally set very low; the intent is to collect any deviation from the protocol dosing rules, and not to specify a medically meaningful cutoff based on PK, PD, or clinical data.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the electronic case report form (eCRF). See Section 10.1 for the immediate reporting of adverse events associated with overdose.

7.2.1.1. CC-220 Overdose

There is no information available about the appropriate dose of CC-220 in humans nor is there any available information regarding overdose. There is no experience in the management of human CC-220 overdose. In the event of overdose, subjects should be managed by symptomatic and supportive care.

7.2.2. Dose Modifications and Interruptions

This is a dose-finding study; therefore, no dose reductions or increases will be permitted. However, in the event a subject experiences a study drug-related adverse event (Section 11.2.3) or abnormal laboratory test (Section 11.2.2), a temporary IP interruption may be required. The Sponsor should be notified in advance of the dosage interruption if possible; however, the decision to interrupt IP dosing will be based on the Investigator's clinical judgment. If a subject missed 4 or more consecutive days of dosing, the Sponsor must be contacted to decide whether dosing should resume or whether the subject should be terminated from the study, return for an Early Termination Visit, and enter into the Observational Follow-up Phase. If a dose of IP is missed, it should be taken as soon as possible on the same day. If the dose is missed for the entire day, the subject should not take an extra dose the next day or take an unscheduled dose.

7.3. Method of Treatment Assignment

Designated study personnel at the investigational sites will be assigned password protected, coded identification, which give them authorization to log on to the IRT to screen and/or randomize subjects, as well as re-supply and discontinue subjects from the study.

After the informed consents have been signed, subjects will be assigned a subject identification (ID) by IRT consisting of a 7-digit number where the first 3 digits are the site ID number concatenated with a 1 and then a 3-digit consecutive run-in number. For example, the first subject entering the study at Site 002 will receive a Subject ID number 0021001. In cases were a subject is screen-failed and later rescreened, the original subject number, concatenated with a "2" is assigned (eg, Subject ID number 0022001). In the event the subject is screen-failed for a second time and then rescreened, the original number, concatenated with a "3" is assigned (eg, Subject ID number 0023001). Confirmation of the subject ID will be sent to the investigational site, the Sponsor and/or its representative.

At the Baseline Visit (Day 1), the system will present a menu of questions by which the study personnel will identify the subject and confirm eligibility. When all questions have been

answered, subjects who meet the eligibility criteria shall be randomized by the IRT to receive either the assigned CC-220 dose or placebo.

Authorized study personal will log into the IRT at each study visit whereupon site personnel will be notified which coded kits to dispense to the subject. The pharmacy or authorized study personnel at the investigational site will dispense coded investigational product kits in accordance with the medication identification number(s) assigned by the IRT.

7.4. Packaging and Labeling

The label(s) for IP will include Sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

The Investigator(s) or designee (s) is responsible for taking an inventory of each IP shipment received. All drug shipments will be acknowledged by the site on the IRT verifying the information contained on the shipping acknowledgement form contained in the shipment/on the IRT shipment acknowledgement screen. The Investigator(s) or designee (s) will retain a copy of the shipping acknowledgement form in the study file.

At the investigational site, all IP will be stored in a locked, safe area to prevent unauthorized access.

Investigational product should be stored according to instructions on the labeled drug product, away from direct sunlight and protected from excessive heat and cold.

7.5. Investigational Product Accountability and Disposal

The Sponsor (or designee) will review with the Investigator and relevant site personnel the process for investigational product and/or medical device materials, if applicable, return, disposal, and/or destruction including responsibilities for the site versus the Sponsor (or designee).

Site staff must make every effort to retrieve all IP supplies from subjects.

7.6. Investigational Product Compliance

Accurate recording of all IP administration (including dispensing and dosing) will be made in the appropriate section of the subject's eCRF and source documents.

Capsules of CC-220 will be counted at every visit starting at Visit 3 through the completion of the study. Overall compliance is defined as taking between 75% and 120% of dispensed IP. In the event of gross compliance problems (eg, missing 4 or more consecutive days of dosing in the absence of a clinically significant adverse event or taking less than 75% or greater than 120% of the doses between study visits) the sponsor must be contacted to decide whether dosing should resume or whether the subject should be terminated from the study and enter into the Observation Follow-up Period.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

This is a Phase 2, randomized, placebo-controlled, double-blind study to evaluate efficacy and safety of three doses of CC-220 in subjects with systemic lupus erythematosus. The treatment assignment will be stratified by Baseline corticosteroid dose (≥ 10 mg/d and < 10 mg/d) and Screening SLEDAI 2K score (≥ 10 points and < 10 points) (Furie, 2016). These proposed strata are to ensure that patients with more severe disease are balanced across treatment groups. This study consists of a 24-week Placebo-Controlled Treatment Phase, a 28-week Double-Blinded Active Treatment Phase, a Long-term Extension Phase of up to 52 weeks, and a 4-week Observational Follow-up Phase with an additional 12-week Observational Follow-Up Visit for males.

This section outlines the statistical analysis strategy and details will be documented in a separate Statistical Analysis Plan (SAP).

9.2. Study Population Definitions

The safety population will include all randomized subjects who received at least one dose of IP. The analysis of safety data in this study will be based on the safety population and subjects will be included in the treatment group they actually received.

The intent-to-treat (ITT) population will include all randomized subjects who receive at least one dose of IP. The analysis of efficacy data in this study will be based on the ITT population unless otherwise specified and subjects will be included in the treatment group to which they are randomized.

The Per Protocol (PP) population will include all randomized subjects who received at least one dose of IP, and have no important protocol deviations that may substantially affect the efficacy results. The final determination of the important protocol deviation criteria will be made prior to the unblinding of the database and will be separately documented.

9.3. Sample Size and Power Considerations

Approximately 280 subjects will be randomized 2:2:1:2 to receive CC-220 (0.45 mg QD, 0.3 mg QD or 0.15 mg QD) or placebo. There will be approximately 80 subjects randomized into each CC-220 0.45 mg QD, CC-220 0.3 mg QD, and placebo arm and approximately 40 subjects into the CC-220 0.15 mg QD arm.

A sample size of 80 subjects in the CC-220 0.45 mg QD, CC-220 0.3 mg QD, and placebo dose groups provides approximately 80% power to detect a true 21% difference (55% versus 34%) between one of the CC-220 group and the placebo group, using a two-group chi-square test with a 0.1 two-sided significance level, for the proportion of subjects achieving an SRI(4) response at Week 24 as defined in Section 2. Based upon clinical trials of Belimumab and Anifrolumab in a similar patient population with SLE, the observed placebo response rate ranged from 34% to 44%. A 21% treatment effect provides a clinically meaningful improvement compared to placebo and approximately 50% higher than the treatment differences achieved in published trials in SLE (Human Genome Sciences, Inc., 2010; Furie, 2016).

The sample size of the 0.15 mg QD dose group is limited to 40 subjects to assess and determine the lowest effective dose and limit the chance of a false negative result. Details of the rationale will be described in the statistical analysis plan (SAP).

9.4. Background and Demographic Characteristics

Subjects' age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while gender, race and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by system organ class and preferred term.

9.5. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent by study phase. A summary of subjects enrolled by site will be provided. Protocol violations and deviations will be summarized using frequency tabulations.

9.6. Efficacy Analysis

No multiplicity adjustment will be conducted for this Phase 2 study. However, in the absence of multiplicity adjustment, p-values and confidence intervals (CIs) from any efficacy analyses should be interpreted with caution. All efficacy analyses will be conducted using the ITT population. The primary efficacy endpoint analysis will be conducted using a PP population in addition to the ITT population (Section 9.2).

9.6.1. Double-blind Placebo-controlled Phase

The primary efficacy endpoint is the SRI(4) response at Week 24. The proportion of subjects who achieve SRI(4) response at Week 24 in each of the CC-220 0.45 mg QD, 0.3 mg QD or 0.15 mg QD groups, will be compared with placebo group using a Cochran-Mantel-Haenszel (CMH) test controlling for corticosteroid dose (≥ 10 mg/d and < 10 mg/d) at Baseline and SLEDAI 2K score (≥ 10 points and < 10 points) at Screening. P-values and 95% confidence intervals for the comparisons will be provided. Missing data for binary endpoints will be handled by nonresponder imputation (NRI), by which a subject will be considered a nonresponder at a given time point if the subject 1) does not have sufficient data (including the Baseline data for the endpoints assessing the change from Baseline) assessed within the analysis visit window for response determination, or 2) has had an event of treatment failure (as per the prespecified criteria) before the date of assessment (or the date of the last assessment in the case of a composite endpoint involving multiple criteria that may be assessed on different dates) for the time point.

Binary variables such as ≥ 50% reduction in CLASI activity score at Week 24 will be analyzed in a similar way to the primary efficacy endpoint.

For continuous endpoints assessed by mean change or percent change from Baseline, a longitudinal data analysis (LDA) model (in the absence of severe departures from normality) or multiple imputation in conjunction with a robust regression that uses M-estimation (in the presence of severe departures from normality) will be used. The LDA model assumes a common

mean across treatment groups at Baseline and a different mean for each treatment group at each of the post-baseline time points. In this model, the response vector consists of the Baseline and post-baseline values for the analysis of the change from Baseline, or the Baseline value and the post-baseline percent changes from Baseline for the analysis of the percent change from Baseline. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. Where specified, the model will also adjust for randomization stratification factors (corticosteroid dose [≥ 10 mg/d and < 10 mg/d] at Baseline, SLEDAI 2K score [≥ 10 points and < 10 points] at Screening).

The time-to-event endpoints will be analyzed by the Kaplan-Meier method, the stratified log-rank test, and the Cox proportional hazards model adjusting for treatment group and randomization stratification factors.

9.6.2. Double-blinded Active Treatment Phase and Long-term Extension Phase

The efficacy endpoints in the Double-Blinded Active Treatment Phase will be analyzed in a similar way to those in the Placebo-Controlled Treatment Phase, except that no formal treatment comparisons will be performed between the CC-220 doses. The efficacy endpoints in the Long-term Extension Phase will be summarized.

9.6.3. Subgroup Analysis

Subgroup analyses for SRI(4) response will be based upon Baseline demographic and disease characteristics. All subgroup analyses will be summarized by individual and pooled (0.45 mg QD and 0.3 mg QD) treatment groups.

9.7. Safety Analysis

The safety analyses will be performed using the safety population as defined in Section 9.2.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system. Adverse events occurring during the 24-week Placebo-Controlled Phase, the 28-week Double-Blinded Active Treatment Phase, and the 4-week Observational Follow-up Phase for females and 12-week Observational Follow-up Phase for males will be tabulated. All adverse events will be summarized by system organ class, preferred term, severity and relationship to IP. Adverse events leading to death or to discontinuation from treatment and serious adverse events will also be tabulated. In the by-subject analysis, a subject having the same event more than once will be counted only once and by greatest severity.

Laboratory data will be summarized by visit descriptively (n, mean, median, standard deviation, minimum, and maximum). In addition, shift tables showing the number of subjects with values low, normal, and high compared to the normal references pretreatment versus posttreatment will be provided. Shift tables will also be provided for ECGs.

Vital sign measurements will be summarized by visit descriptively (n, mean, median, standard deviation, minimum, and maximum). In addition, shift tables showing the number of subjects with values low, normal, and high compared to the normal reference ranges pretreatment versus posttreatment will be provided.

9.8. Interim Analysis

Unblinded interim analyses may be performed by a group that is independent of the study team. The purpose of the interim analysis is to determine if any treatment group should be discontinued, and whether to terminate the study for futility. The interim analysis will be conducted after approximately 50 percent of the subjects have completed or discontinued prior to the Week 24 Visit. The details of this analysis including the scope of distribution will be documented in a separate charter/analysis plan.

9.9. Other Topics

[redacted]

9.9.4. Independent External Data Monitoring Committee

Although the Sponsor study staff will monitor safety on an ongoing basis throughout the study, formal blinded safety assessments of the relevant study data will be performed by an external independent Data Monitoring Committee (DMC). The DMC will review unblinded data to evaluate safety during the study and data from the interim analysis for futility. The DMC is comprised of independent physician experts and a statistician for whom there is no identified conflict of interest. The DMC will be convened regularly, at least once a year, or ad hoc at the request of the SMT. Recommendations of the DMC based on the overall benefit/risk evaluation may include proceeding with the study per protocol, proceeding with the study with modification, or study suspension. The scope, conduct, membership, processes, and accountabilities of the DMC are specified in the DMC charter.

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (eg, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Worsening of a subject's SLE or SLE flares should be considered as worsening of the disease under study and not recorded as an AE unless the event meets the definition of a SAE (Section 6.8.1).

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF. (See Section 7.2.1 for the definition of overdose.) Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE CRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE CRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and CRF but should not be reported as an SAE itself.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for CC-220 overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent until 28 days after the last dose of IP as well as those SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP. AEs and SAEs will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

10.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

10.2.1. Seriousness

An SAE is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (eg, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- a standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- the administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- a procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- a procedure that is planned (eg, planned prior to start of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- an elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, that has not worsened from Baseline.
- emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to the IP, action taken regarding the IP, and outcome.

10.2.2. Severity/Intensity

For both AEs and SAEs, the Investigator must assess the severity/ intensity of the event.

Mild

- Asymptomatic or mild symptoms; clinical or diagnostic observations only
- Intervention not indicated
- Activities of daily life (ADLs) minimally or not affected
- No or minimal intervention/therapy may be required

Moderate

- Symptom(s) cause moderate discomfort
- Local or noninvasive intervention indicated
- More than minimal interference with ADLs but able to carry out daily social and functional activities.
- Drug therapy may be required

Severe (could be non-serious or serious)

- Symptoms causing severe discomfort/pain
- Symptoms requiring medical/surgical attention/intervention
- Interference with ADLs including inability to perform daily social and functional activities (eg, absenteeism and/or bed rest)
- Drug therapy is required

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.2.3. Causality

The Investigator must determine the relationship between the administration of the IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	a causal relationship of the adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	there is a **reasonable possibility** that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by the Sponsor, please provide the name of the manufacturer when reporting the event.

10.2.4. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

10.2.5. Action Taken

The Investigator will report the action taken with IP as a result of an AE or SAE, as applicable (eg, discontinuation or interruption, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6. Outcome

The Investigator will report the outcome of the event for both AEs and SAEs.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, or death (due to the SAE).

10.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or

- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

10.4. Pregnancy

All male and female subjects should be counseled about pregnancy precautions and risks of fetal exposure as described in the Pregnancy Prevention Plan (provided separately).

All pregnancies or suspected pregnancies occurring in either a female subject of childbearing potential or partner of childbearing potential of a male subject are immediately reportable events.

In the event of a pregnancy occurring in a female subject of childbearing potential or female partner of a male subject, Celgene will follow up with the clinical Investigator each trimester of pregnancy and for 1 year following the birth of the infant (if applicable). Please reference the pregnancy information consent (permission) forms for data collection for additional information.

The exposure of any pregnant female (eg, caregiver, pharmacist, study coordinator or monitor) to CC-220 is also an immediately reportable event.

10.4.1. Females of Childbearing Potential:

Pregnancies and suspected pregnancies (including elevated β-hCG or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on CC-220, or within 28 days of the subject's last dose of CC-220, are considered immediately reportable events. Investigational product is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

10.4.2. Male Subjects

If a female partner of a male subject taking IP becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

10.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the CRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method (eg, via email), using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until 28 days after the last dose of IP) or any SAE made known to the Investigator at any time thereafter that are suspected of being related to IP. Serious adverse events occurring prior to treatment (after signing the ICF) will be captured.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with the Sponsor and the IRB/EC.

10.5.1. Safety Queries

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

10.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to CC-220 based on the Investigator Brochure.

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

For countries within the European Economic Area, the Sponsor or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, SUSARs in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

The Sponsor or its authorized representative shall notify the Investigator of the following information:

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (eg, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with the Sponsor and the IRB/EC. (See Section 14.3 for record retention information).

Celgene Drug Safety Contact Information:

For Celgene Drug Safety contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.

11. DISCONTINUATIONS

11.1. Discontinuations

The following events are considered sufficient reasons for discontinuing a subject from the investigational product and/or from the study:

- Adverse event
- Lack of efficacy
- Non-compliance with study drug
- Withdrawal of consent by subject
- Study terminated by the sponsor
- Protocol violation
- Death
- Lost to follow-up
- Other (to be specified on the CRF)

The reason for discontinuation of treatment should be recorded in the CRF and in the source documents.

The decision to discontinue a subject from treatment remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

11.2. Investigational Drug Interruption and Stopping Rules

11.2.1. Pregnancy

Any subject who is pregnant or has a positive pregnancy test must be discontinued immediately from the study. The subject must complete an Early Termination Visit as soon as possible and enter the Observational Follow-up Phase.

Any subject who has a borderline positive serum pregnancy test must hold IP and repeat the serum pregnancy test. If the repeat pregnancy test remains borderline, consult the Medical Monitor.

If pregnancy or a positive pregnancy test occurs in the partner of a male subject, the Investigator must be notified immediately.

11.2.2. Laboratory

- Absolute Neutrophil Count (ANC) < 500 cells/μL (with or without signs or symptoms of infection):
    - IP must be held immediately and the neutrophil count retested as soon as possible, preferably within 3 days. If the retest is < 500 cells/μL, the subject

must be discontinued from the study. If the retest is ≥ 500 cells/μL, the subject should continue to hold IP until the ANC rises above 1000 cells/μL, while retesting the neutrophil counts weekly, or as determined necessary based on the level of neutropenia. The IP can be resumed once the neutrophil count is ≥ 1000 cells/μL.

- ANC ≥ 500 cells/μL and < 1000 cells/μL without signs or symptoms of infection:
  - IP should be held until the ANC rises above 1000 cells/μL, while retesting the neutrophil counts weekly, or as determined necessary based on the level of neutropenia. If the ANC falls < 500 cells/μL, the subject must be discontinued from the study. The IP can be resumed once the neutrophil count is ≥ 1000 cells/μL.
- ANC ≥ 500 cells/μL and < 1000 cells/μL with signs or symptoms of infection:
  - IP must be held immediately, and the neutrophil count retested as soon as possible, preferably within 3 days. The Investigator should discuss with the Medical Monitor if the subject should continue study participation.
- If the neutrophil count drops repeatedly below 1000 cells/μL after IP is resumed, or the neutrophil count remains below 1000 cells/μL after 4 weeks off IP, the Investigator should discuss with the Medical Monitor if the subject should continue study participation.
- If growth factors must be administered during any IP dose interruption triggered by low ANC, the subject should be discontinued from the study.
- Subjects who are discontinued from the study must complete an Early Termination Visit as soon as possible, and enter the Observational Follow-up Phase.

For any questions regarding abnormal laboratory values, the investigator may contact the Medical Monitor.

11.2.3. AEs/SAEs

Subjects who develop one of the following AEs/SAEs must be discontinued:

- A thromboembolic event (eg, deep vein thrombosis, pulmonary embolism, thrombotic cerebrovascular or cardiovascular events). In such events, an antiphospholipid panel should be collected, if possible, before initiation of any therapy.

Subjects who develop one of the following AEs/SAEs, should suspend IP and contact the Medical Monitor to discuss continued eligibility of the subject:

- Recurrent infections or systemic opportunistic infections requiring hospitalization and/or parenteral antibiotics
- Life-threatening or disabling rash or blistering
  - Subjects may have a skin biopsy to confirm if the rash is not a manifestation of the disease under study (SLE).
- Uveitis or other clinically significant ophthalmological findings

11.2.4. Study Stopping Criteria

In the event that > 3% of subjects exposed to CC-220 experience a ≥ Grade 3 thromboembolic event or > 5% of subjects exposed to CC-220 experience a ≥ Grade 2 thromboembolic event (as defined by CTCAE version 4.03) (Appendix Q):

- All screening and randomization activities will be suspended
- IP will be held for all enrolled subjects
- The DMC will be convened to assess the risk/benefit of IP. The final decision on study continuation will be made by the Sponsor in consultation with the DMC.

12. EMERGENCY PROCEDURES

12.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call the Sponsor/contract research organization Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

12.2. Emergency Identification of Investigational Products

The blind must not be broken during the course of the study **unless** in the opinion of the Investigator, it is absolutely necessary to safely treat the subject. If it is medically imperative to know what IP the subject is receiving, IP should be temporarily discontinued if, in the opinion of the Investigator, continuing IP can negatively affect the outcome of the subject's treatment.

The decision to break the blind in emergency situations remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, the Investigator may contact the Medical Monitor prior to breaking the blind to discuss unblinding, mainly in the interest of the subject.

The Investigator should ensure that the code is broken only in accordance with the protocol. The Investigator should promptly notify the Medical Monitor of the emergency unblinding and the reason for breaking the blind, which should be clearly documented by the Investigator in the subject's source documentation.

Emergency unblinding should only be performed by the Investigator or designee as indicated in the Delegation of Authority log. The Investigator or designee will log into the IRT to perform emergency unblinding in order to obtain the subject's unblinded dose information.

13. REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor, its authorized representative, and Investigator abide by GCP, as described in ICH Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

13.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Sponsor staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of Sponsor information. The Investigator should maintain a list of Sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an informed consent form (ICF) and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of CRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by the Sponsor on public registry websites) is considered Sponsor confidential information. Only information that is previously disclosed by the Sponsor on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. The Sponsor protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from the Sponsor. Information proposed for posting on the Investigator's or their institution's website must be submitted to the Sponsor for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, the Sponsor will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

13.3. Subject Information and Informed Consent

The Investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original ICF signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the ICF must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF. The revised ICF signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

13.4. Confidentiality

The Sponsor affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). The Sponsor requires the Investigator to permit the Sponsor's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

13.5. Protocol Amendments

Any amendment to this protocol must be approved by the Sponsor's Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

13.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

IP can only be supplied to an Investigator by the Sponsor or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by

the Sponsor or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by the Sponsor and the IRB/EC prior to use.

13.7. Ongoing Information for Institutional Review Board/ Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

13.8. Termination of the Study

The Sponsor reserves the right to terminate this study prematurely at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc).

In addition, the Investigator or the Sponsor has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

14. DATA HANDLING AND RECORDKEEPING

14.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

14.2. Data Management

Data will be collected via CRF and entered into the clinical database per the Sponsor's Standard Operating Procedures (SOPs). This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

14.3. Record Retention

Essential documents must be retained by the Investigator according to the period of time outlined in the clinical trial agreement. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, the Sponsor, and their authorized representative(s);
- List of Sub-Investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);

- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify the Sponsor if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from the Sponsor prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask the Sponsor for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator or institution should take measures to prevent accidental or premature destruction of these documents.

15. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by the Sponsor or its authorized representative for compliance with applicable government regulations with respect to current GCP and SOPs.

15.1. Study Monitoring and Source Data Verification

The Sponsor ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigators' Meeting. Prior to enrolling subjects into the study, a Sponsor representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Sponsor representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

15.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within the Sponsor. Representatives of this unit will conduct audits of clinical research activities in accordance with Sponsor SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, FDA, EMA, Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact the Sponsor immediately.

15.3. Product Quality Complaint

A Product Quality Complaint (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, purity, or performance of any drug product manufactured by or on behalf of Celgene Corporation after it is released for distribution. The PQCs may reduce the usability of the product for its intended function or affect performance of the product and therefore, pose a significant risk to the patient. Examples of PQCs include (but are not limited to): mixed product, mislabeling, lack

of effect, seal/packaging breach, product missing/short/overage, contamination, suspected

16. PUBLICATIONS

As described in Section 13.2, all protocol- and amendment-related information, with the exception of the information provided by the Sponsor on public registry websites, is considered Sponsor confidential information and is not to be used in any publications. Sponsor protocol-related information proposed for use in a publication must be submitted to the Sponsor for review and approval, and should not be utilized in a publication without express written approval from the Sponsor, or as described in the Clinical Trial Agreement.

The Sponsor will ensure Celgene-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses, and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.

18. APPENDICES

APPENDIX A. ABBREVIATIONS

Table 7: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ACR	American College of Rheumatology
ADLs	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
ANA	Antinuclear antibody
ANC	Absolute neutrophil count
APS	Antiphospholipid Syndrome
AST	Aspartate aminotransferase (SGOT)
ATEP	Active Treatment Extension Phase
AUC	Area under the curve
β-hCG	β-subunit of human chorionic gonadotropin
BILAG	British Isles Lupus Assessment Group
CBC	Complete blood count
CD	Cluster of differentiation
CFR	Code of Federal Regulations
CI	Confidence interval
CLASI	Cutaneous Lupus Area and Severity Index
C_{max}	Maximum plasma concentration of drug
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CPPCP	Celgene Pregnancy Prevention Counseling Program
CRBN	Cereblon
CRF	Case report form
CT	Computed tomography
DMC	Data Monitoring Committee
ds-DNA	Double-stranded deoxyribonucleic acid
EC	Ethics Committee

Table 7: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ESR	Erythrocyte sedimentation rate
FACIT	Functional Assessment of Chronic Illness Therapy
FCBP	Female of child bearing potential
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HAQ-DI	Health assessment questionnaire – disability index
HIV	Human immunodeficiency virus
Hs-CRP	High sensitivity – c-reactive protein
IA	Intra-articular
ICF	Informed consent form
ICH	International Council for Harmonisation
ID	Identification
IFN	Interferon
Ig	Immunoglobulin
IKZF	Ikaros
IL	Interleukin
IM	Intramuscular
IND	Investigational New Drug
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-treat
IV	Intravenous
LDA	Longitudinal data analysis
LH	Luteinizing hormone

Table 7: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
LupusPRO	Lupus patient reported outcome
MAF	Minor allele frequency
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
mRNA	Messenger ribonucleic acid
NSAID	Nonsteroidal anti-inflammatory drug
PA	Posterior-anterior
PBMCs	Peripheral blood mononuclear cells
PCS	Physical Component Summary
PD	Pharmacodynamic
pDC	Plasmacytoid dendritic cell
PG	Pharmacogenetic
PGA	Physician's Global Assessment
PK	Pharmacokinetic
PO	Oral
PP	Per protocol
PQC	Product Quality Compliant
OCS	Oral corticosteroid dose
QD	Once a day
QOL	Quality-of- life
OR	Odds ratio
RBC	Red blood cell
RNP	Ribonucleoprotein
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SF-36	Short Form-36

Table 7: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SLE	Systemic lupus erythematosus
SLEDAI (2K)	Systemic Lupus Erythematosus Disease Activity Index (2K)
SLICC/ACR	Systemic Lupus International Collaborating Clinics/American College of Rheumatology
SMT	Safety management team
SNP	Single nucleotide polymorphism
SOP	Standard operating procedure
SRI	Systemic lupus erythematosus Responder Index
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Half-life
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
Tfh	Follicular helper T cells
Th	T cell helper
TNF-α	Tumor necrosis factor-alpha
ULN	Upper limit of normal
US	United States
VAS	Visual analog scale
WBC	White blood cell