DISCLOSURE

REDACTED PROTOCOL AMENDMENT 6

CC-220-SLE-001

A PILOT, PHASE 2, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND, STUDY TO EVALUATE EFFICACY, SAFETY, TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS AND PHARMACOGENETICS OF CC-220 IN SUBJECTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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PROTOCOL SUMMARY

Study Title

A Pilot, Phase 2, Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Efficacy, Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Pharmacogenetics of CC-220 in Subjects with Systemic Lupus Erythematosus

Indication

Systemic Lupus Erythematosus (SLE)

Objectives

Part 1

- Primary:
  - To evaluate the safety and tolerability of CC-220 for subjects with SLE
- Secondary:
  - To describe the pharmacokinetics (PK) of CC-220 for subjects with SLE
- CCI [redacted]

Active Treatment Extension Phase

- Primary:
  - To evaluate the long-term safety and tolerability of CC-220 in subjects with SLE who completed Part 1 of the core study
- Secondary:
  - To evaluate the long-term efficacy of CC-220 in subjects with SLE who completed Part 1 of the core study
- CCI [redacted]

Study Design

This is a pilot, Phase 2, randomized, placebo-controlled, double-blind, multicenter study to evaluate the preliminary efficacy, safety, tolerability, pharmacokinetics, pharmacodynamics and pharmacogenetics of CC-220 in SLE subjects with skin involvement.

This study will be conducted in two parts.

Part 1

Part 1 is a randomized, double-blind, placebo-controlled, ascending dose study to evaluate the safety and tolerability of CC-220 in SLE subjects.

Subject participation in Part 1 will consist of 3 phases:

- Pre-treatment Screening Phase: up to 42 days prior to the first dose of the investigational product (IP)
- Treatment Phase: up to 84 days
- Observational Follow-up Phase: 84 day post-treatment (subjects who consent and qualify for the Active Treatment Extension Phase [ATEP] will NOT enter the Observational Follow-up Phase and will directly enter the ATEP)

A total of approximately 40 subjects will be randomized into 4 dose groups with a 4:1 ratio of CC-220 (0.3 mg every other day [QOD], 0.3 mg everyday [QD], 0.6 mg and 0.3 mg on alternating days and 0.6 mg QD) or matching placebo (8 subjects in the CC-220 arm and 2 subjects in the placebo arm for each dose group) using an Interactive Voice Response System (IVRS). Subjects will be randomized into the first two dose groups of 0.3 mg QOD and 0.3 mg QD in parallel. Following confirmation of safety of the first two dose groups, remaining subjects will then be randomized into the 0.6 mg and 0.3 mg on alternating days and 0.6 mg QD dose groups in a sequential, dose-ascending manner (first the 0.6 mg and 0.3 mg on alternating days dose group followed by the 0.6 mg QD dose group). The Treatment Phase will be up to 84 days in duration for all dose groups. Subjects who discontinue IP early and all subjects who complete the 84-day Treatment Phase (who do not consent to enroll into the ATEP) will enter into the Observational Follow-up Phase for an 84-day period. In all cases of early termination from the study, subjects will be encouraged to complete an Early Termination Visit. See Figure 1 for graphical representation of the Part 1 dosing administration schedule.

All subjects will be allowed to remain on stable doses of hydroxychloroquine, chloroquine, and/or quinacrine for ≥ 4 weeks prior to their baseline visit and throughout the study. No additional systemic immunosuppressives will be permitted. In addition, as needed (PRN) treatment with systemic anti-pruritics and/or systemic analgesics will be permitted; subjects must stop using all systemic anti-pruritics 48 hours prior to all study visits and systemic analgesics 12 hours prior to all study visits. Oral non-steroidal anti-inflammatory drugs (NSAIDs) may be used, but must be stopped 12 hours prior to all study visits. Use of oral corticosteroids will be permitted only at doses of 10 mg or less per day and must be maintained at a stable dose during study participation. Inhaled corticosteroids for use in a disease other than lupus, eg, asthma, will be allowed. No IV (intravenous) or IM (intramuscular) corticosteroids will be permitted during the study. No other topical (with the exception of potency class 6 and 7 topicals only), local or systemic treatments for dermatological manifestations of SLE will be permitted.

Following completion of the first 28 days of the treatment phase by at least 8 subjects in Dose Group 1 (0.3 mg QOD) and 8 subjects in Dose Group 2 (0.3 QD), an assessment of safety and tolerability will be conducted. If Dose Groups 1 and 2 are deemed to have acceptable safety and tolerability, subjects will continue to receive investigational product for up to 84 days and enrollment of subjects into Dose Group 3 (0.6 mg and 0.3 mg on alternating days) will be

initiated. Following completion of the first 28 days of the treatment phase by at least 8 subjects in Dose Group 3 (0.6 mg and 0.3 mg on alternating days), an assessment of safety and tolerability will be conducted. If Dose Group 3 is deemed to have acceptable safety and tolerability, subjects will continue to receive investigational product for up to 84 days and enrollment of subjects into Dose Group 4 (0.6 mg QD) will be initiated. Following completion of the first 28 days of the treatment phase by at least 8 subjects in Dose Group 4 (0.6 mg QD), an assessment of safety and tolerability will be conducted. If Dose Group 4 is deemed to have acceptable safety and tolerability, subjects will continue to receive investigational product for up to 84 days.

Subjects will remain on their assigned treatment for up to 84 days. In the event a subject experiences clinically significant IP-related adverse events (AEs), a dose interruption for up to 14 days will be permitted (see Section 12.1). If a subject is unable to remain on their assigned dose, he/she may reduce their dose to the next lowest dosing regimen. Dose reductions will occur as follows:

- Subjects on 0.6 mg QD will reduce their dose to 0.6 mg/0.3 mg on alternating days
- Subjects on 0.6 mg/0.3 mg on alternating days will reduce their dose to 0.3 mg QD
- Subjects on 0.3 mg QD will reduce their dose to 0.3 mg QOD
- Subjects on 0.3 mg QOD will reduce their dose to placebo

A subject will only be permitted to reduce their dose one time during the study. The decision to modify IP dosing will be based on the rules provided in Section 12.1. The sponsor should be notified of the intent to dose reduce prior to a change in dosing.

Subjects who discontinue from the study prior to completing 28 days of treatment may be replaced (for up to a total of 10 subjects for Part 1) at the discretion of the sponsor.

Active Treatment Extension Phase

The ATEP is an extension of the core CC-220-SLE-001 study to evaluate the long-term efficacy and safety/tolerability of CC-220 in SLE subjects who completed Part 1 of the core study.

Subjects who complete the Treatment Phase of Part 1 of the core study will be eligible to receive CC-220 in the ATEP for up to 2 years. All subjects who participate in the ATEP will receive the same active treatment they received during their participation in Part 1 with the exception of those on placebo or 0.3 mg QOD (see below for information on dosing for these subjects).

Subjects who complete the Treatment Phase of Part 1 of the core study will be eligible to enter this phase of the study and should be enrolled immediately to avoid dose interruption. In the event the ATEP has not been implemented by a subject's study center at the time they have completed the Treatment Phase, subjects will enter the Observation Phase of the core study and be eligible to enroll in the ATEP upon implementation of this amendment. There are no time restrictions on how long subjects can be off CC-220 prior to entering the ATEP as long as they completed treatment in Part 1 of the core study, but with the implementation of Protocol Amendment 5, enrollment into the ATEP is now closed. Subjects who terminate the Treatment Phase of Part 1 early will not be eligible for entry into the ATEP.

Subject participation consists of two phases:

- Active Treatment Extension Phase: Up to 2 years
- Observational Follow-up Phase: 28 days

Subjects receiving CC-220 0.3 mg QOD or CC-220 0.3 mg QD during their participation in the core study will be assigned to receive CC-220 0.3 mg QD during the ATEP. Subjects receiving CC-220 0.6 mg/0.3 mg on alternating days during their participation in the core study will remain on the same assigned dose during the ATEP. Subjects receiving CC-220 0.6 mg QD during their participation in the core study were originally permitted to enter the ATEP on the same dose. However, based on data that has become available for Part 1 (see Section 4.2.3), any subject originally enrolled in the ATEP on the 0.6 mg QD dose should be dose reduced to the 0.6 mg/0.3 mg on alternating days dose upon implementation of Protocol Amendment 5.

Subjects receiving placebo during their participation in the core study (Part 1) will receive the CC-220 dose given to those on active drug in their respective cohort. For example, if a subject was taking placebo in Dose Group 3 of Part 1, he or she would receive CC-220 0.6 mg/0.3 mg on alternating days during the ATEP. However, based on data that has become available for Part 1 (see Section 4.2.3), any subject who was on placebo in the 0.6 mg QD cohort for Part 1 and originally entered the ATEP on 0.6 mg QD should be dose reduced to 0.6/0.3 mg QD on alternating days upon implementation of Protocol Amendment 5.

For subjects who are eligible to roll directly into the ATEP, Week 12 (Visit 10) of Part 1 may be on the same day as Visit 1 of the ATEP. All Visit 10 (Part 1) and Visit 1 (ATEP) procedures must be conducted as outlined in Table 1 and Table 2. Please note that subjects rolling directly into the ATEP who have both Week 12 (Visit 10) of Part 1 and Visit 1 of the ATEP on the same day, will only undergo a subset of assessments for Visit 1 of the ATEP (indicated in Table 2). If the subject remains eligible for entry into the ATEP following Visit 1 assessments, drug will be dispensed and the subject will begin the ATEP. Subjects entering the ATEP who cannot hold their Week 12 (Visit 10) of Part 1 and Visit 1 of the ATEP on the same day, can hold their Visit 1 of the ATEP at any time after their sites has received IRB approval. **However**, **once 14 days have elapsed since a subject has had their Part 1 Week 12 (Visit 10), they must undergo the ATEP Screening Visit and all assessments listed for Visit 1 of the ATEP in** Table 2 **if they wish to enter the ATEP. As long as a subject comes in for their Visit 1 ATEP within 14 days after their Part 1 Week 12 (Visit 10) they will only need to complete the subset of assessments identified under footnote b of** Table 2**.**

All subjects will be allowed to remain on stable doses of hydroxychloroquine, chloroquine, and/or quinacrine for ≥ 4 weeks prior to their baseline visit and throughout the study. Subjects on antimalarials will be permitted to modify or stop their treatment at any time during the ATEP. Methotrexate (7.5 mg – 25 mg per week), leflunomide (maintenance dosing must not exceed 20 mg daily) or sulfasalazine (dosing not to exceed 3g daily) will be permitted, although no other additional systemic immunosuppressives will be permitted. In addition, PRN treatment with systemic anti-pruritics and/or systemic analgesics will be permitted. However, subjects must stop using all systemic anti-pruritics 48 hours prior to all study visits and systemic analgesics 12 hours prior to all study visits. Oral NSAIDs may be used, but must be stopped 12 hours prior to all study visits. Use of oral corticosteroids will be permitted at doses of 10 mg or less per day and ideally should be maintained at a stable dose during study participation. Inhaled corticosteroids

for use in a disease other than lupus, eg, asthma, will be allowed. No IV or IM corticosteroids will be permitted during the study. No other topical (with the exception of potency class 6 and 7 topicals only), local or systemic treatments for dermatological manifestations of SLE will be permitted.

Thromboprophylaxis with low dose aspirin, low molecular weight heparin or other equivalent antithrombotic or anticoagulant is required unless the investigator determines that, based on the totality of the subjects' risk factors for thrombosis, thromboprophylaxis is not required or is contraindicated.

If any additional prophylaxis is needed, it should be based on the local standard of care and the investigator's best judgement after careful consideration of the benefit versus the potential risk for the individual subject.

Subjects will remain on their assigned treatment for up to 2 years. In the event a subject experiences clinically significant IP-related AEs, a dose interruption for up to 14 days will be permitted (see Section 12.1). If a subject is unable to remain on their assigned dose, he/she may reduce their dose to the next lowest dosing regimen. Dose reductions will occur as follows:

- Subjects on CC-220 0.6 mg QD will reduce their dose to CC-220 0.6 mg/0.3 mg on alternating days
- Subjects on CC-220 0.6 mg/0.3 mg on alternating days will reduce their dose to CC-220 0.3 mg QD
- Subjects on CC-220 0.3 mg QD will be terminated from the study

A subject will only be permitted to reduce their dose one time during the study (subjects who originally came into the ATEP on 0.6 mg QD and dose reduce to 0.6/0.3 mg QD on alternating days upon implementation of Protocol Amendment 5 will be eligible for one additional dose reduction in the ATEP). The decision to modify IP dosing will be based on the rules provided in Section 12.1. The sponsor should be notified of the intent to dose reduce prior to a change in dosing.

Subjects will have regularly scheduled visits to assess IP activity and safety. Required assessments will be completed as depicted in Table 2.

Upon completion of, or discontinuation from the ATEP, all subjects (including premature discontinuations) will enter a 28 day Observational Follow-up Phase. Subjects who discontinue IP early should complete an Early Termination Visit.

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and applicable regulatory requirements.

Study Population

The study population consists of male and female subjects 18 years of age and older at the time of signing the informed consent document (ICD).

Subjects in Part 1 are required to have:

An established diagnosis of SLE as defined by the 1997 Update of the 1982 American College of Rheumatology (ACR) Revised Criteria for Classification of SLE at Screening (Appendix D) and

a minimum Hybrid SELENA Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score of ≥ 4 points.

Subjects in the Active Treatment Extension Phase are required to have:

- Completed the CC-220-SLE-001 core study (Part 1).

Length of Study

The length of study participation for each subject in Part 1 is 210 days (Up to a 42-day Screening Phase, 84-day Treatment Phase and an 84-day Observational Follow-Up Phase). The length of study participation for each subject in the ATEP is up to 2 years and 1 month (up to a 2-year ATEP and a 28-day post-treatment Observational Follow-Up Phase). Subjects who participate in both Part 1 and the ATEP will participate in the study for a total of approximately 2 years and 6 months.

The End of Trial is defined as either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analyses, as pre-specified in the protocol and/or the Statistical Analysis Plan, whichever is the later date.

Study Treatments

CC-220 will be provided as 0.3 mg capsules. Standard matching placebo capsules will also be provided. Capsules will be taken by mouth (PO) with or without food.

Subjects will be randomized to one of the 4 following dose groups for Part 1. The ATEP will allow for subjects to continue on the dose they were administered during their involvement in the core study (with the exception of subjects on CC-220 0.3 mg QOD or placebo who will be re-assigned as described in the Study Design above). Subjects receiving CC-220 0.6 mg QD during their participation in the core study were originally permitted to enter the ATEP on the same dose. However, based on data that has become available for Part 1 (see Section 4.2.3), any subject originally enrolled in the ATEP on the 0.6 mg QD dose should be dose reduced to the 0.6 mg/0.3 mg on alternating days dose upon implementation of Protocol Amendment 5. Investigational product will be administered PO as described below:

CC-220

- 0.3 mg QOD (Part 1 only)

  Subjects will receive 0.3 mg once every other day
- 0.3 mg QD

  Subjects will receive 0.3 mg every day
- 0.6 mg and 0.3 mg on alternating days

  Subjects will receive 0.6 mg and 0.3 mg on alternating days.
- 0.6 mg QD

  Subjects will receive 0.6 mg every day

Placebo (Part 1 only)

Subjects assigned to the placebo group will receive matching placebo capsule(s) daily.

In the event a subject experiences clinically significant IP-related AEs, a dose interruption for up to 14 days will be permitted (see Section 12.1). If a subject is unable to remain on their treatment, the subject will either be dose reduced or discontinue IP early and enter into an 84-day Observational Follow-up Phase. In the case of a dose reduction, subjects on placebo will be reduced to placebo to maintain the blind. In all cases of early termination from the study, subjects will be encouraged to complete an Early Termination Visit. The decision to modify IP dosing will be based on the rules provided in Section 12.1. The sponsor should be notified of the intent to dose reduce prior to a change in dosing.

In the event that a subject experiences a flare during the Observational Follow-up Period, the Investigator may treat the subject with the standard of care in order to allow the subject to remain in the Observational Follow-up Period and continue with the scheduled visits and assessments indicated by the schedule of assessments.

There will be no placebo in the ATEP.

The safety assessments may be conducted by a physician, physician assistant, nurse practitioner, or study nurse. Ideally, the safety assessor should be the same individual throughout the course of each subject's participation at a site. The efficacy assessments must be conducted by a physician, physician assistant, or qualified nurse practitioner. The trained investigator/sub-investigator conducting efficacy assessments should remain the same throughout the study.

Overview of Safety Assessments

- Adverse events
- Vital signs, including height, weight, pulse, temperature and blood pressure
- Hematology, chemistry, urinalysis
- Inflammation panel
- Serum beta-human chorionic gonadotropin (HCG) and urine pregnancy tests (for females of childbearing potential [FCBP])
- Tetanus toxoid vaccine, pneumococcal antigen and influenza titers
- Centralized 12-lead electrocardiograms (ECGs)
- Physical examinations, including height and weight
- Concomitant medications and procedures
- Ophthalmological examinations will be conducted by a qualified ophthalmologist. Testing will include visual acuity and slit lamp exams with fluorescein staining following pupillary dilation, focusing on the anterior chamber, iris and anterior vitreous (unless use of fluorescein is contraindicated, eg, due to hypersensitivity).
- Hepatitis screening
- Testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH) **for males only**

- Amylase and lipase

Overview of Pharmacokinetic Assessments

Blood samples for quantification of CC-220 in plasma will be taken at specified timepoints (Table 1) during the course of the study.

Approximately 4 subjects in each of the 4 treatment groups in Part 1 (a targeted total of 32 subjects) will be identified for participation in the Intensive PK sub-study. The IVRS will be used to identify for inclusion approximately 4 intensive PK participants per dose group. Noncompartmental PK parameters of CC-220 will be estimated from these subjects.

All other subjects who do not participate in the Intensive PK sub-study will have sparse PK samples collected.

No PK will be assessed during the ATEP.

CCI [redacted]

Overview of Efficacy Assessments

- Cutaneous Lupus Area and Severity Index (CLASI) (Appendix A)
- Hybrid SELENA Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (Appendix E)
- Physician's Global Assessment (PGA) (Appendix C)
- Swollen and Tender Joint Counts (Appendix B)
- Pericardial/Pleuritic Pain Numerical Rating Scale (Appendix G)
- Systemic Lupus International Collaborating Clinics/American College of Rheumatology Systemic Lupus Erythematosus (SLICC/ACR SLE) Damage Index (Appendix O)
- British Isles Lupus Assessment Group 2004 (BILAG) (Appendix P)

CCI [redacted]

- [redacted]
- [redacted]
- [redacted]

TABLE OF CONTENTS

TITLE PAGE 1
PROTOCOL SUMMARY 6
1. INTRODUCTION 22
2. STUDY OBJECTIVES 27
2.1. Part 1 27
2.1.1. Primary 27
2.1.2. Secondary 27
CCI [redacted]
2.2. Active Treatment Extension Phase 27
2.2.1. Primary 27
2.2.2. Secondary 27
CCI [redacted]
3. STUDY ENDPOINTS 28
3.1. Part 1 28
3.1.1. Primary 28
3.1.2. Secondary 28
CCI [redacted]
3.2. Active Treatment Extension Phase 29
3.2.1. Primary 29
3.2.2. Secondary 29
CCI [redacted]
4. OVERALL STUDY DESIGN 31
4.1. Study Design 31
4.2. Study Design Rationale 35
4.2.1. Duration of Treatment 35
4.2.2. Study Population 35
4.2.3. Dose and Dose Interval 35
4.2.4. Blinding 36
4.2.5. Concomitant Medications 36
4.2.6. Efficacy 37
4.2.7. Safety 37

4.2.7.1. Internal Celgene Monitoring at the Study Level 39
4.2.7.2. Internal Celgene Safety Monitoring of CC-220 at the Compound Level – Role of the Safety Management Team 39
4.2.8. Pharmacokinetic CCI [redacted] Markers 39
4.3. Study Duration 41
4.4. End of Trial 41
5. TABLE OF EVENTS 42
6. PROCEDURES 50
7. STUDY POPULATION 59
7.1. Number of Subjects and Sites 59
7.2. Inclusion Criteria 59
7.2.1. Part 1 59
7.2.2. Active Treatment Extension Phase 61
7.3. Exclusion Criteria 62
7.3.1. Part 1 and Active Treatment Extension Phase 62
8. DESCRIPTION OF STUDY TREATMENTS 66
8.1. Description of Investigational Product(s) 66
8.2. Treatment Administration and Schedule 66
8.2.1. Dose Modification or Interruption 66
8.2.2. Overdose 67
8.3. Method of Treatment Assignment 67
8.4. Packaging and Labeling 67
8.5. Investigational Product Accountability and Disposal 68
8.6. Investigational Product Compliance 68
9. CONCOMITANT MEDICATIONS AND PROCEDURES 69
9.1. Permitted Concomitant Medications and Procedures 69
9.2. Prohibited Concomitant Medications and Procedures 70
9.3. Required Concomitant Medications and Procedures 70
10. STATISTICAL ANALYSES 71
10.1. Overview 71
10.2. Study Population Definitions 71
10.3. Sample Size and Power Considerations 71
10.4. Background and Demographic Characteristics 72

10.5. Subject Disposition 72
10.6. Efficacy Analysis 72
10.7. Safety Analysis 73
10.8. Interim Analysis 73
10.9. Other Topics 73
10.9.1. Pharmacokinetic Analysis 73
CCI [redacted]
11. ADVERSE EVENTS 75
11.1. Monitoring, Recording and Reporting of Adverse Events 75
11.2. Evaluation of Adverse Events 75
11.2.1. Seriousness 75
11.2.2. Severity / Intensity 77
11.2.3. Causality 77
11.2.4. Duration 78
11.2.5. Action Taken 78
11.2.6. Outcome 78
11.3. Abnormal Laboratory Values 78
11.4. Pregnancy 79
11.4.1. Females of Childbearing Potential 79
11.4.2. Male Subjects 79
11.5. Reporting of Serious Adverse Events 79
11.5.1. Safety Queries 80
11.6. Expedited Reporting of Adverse Events 80
12. DISCONTINUATIONS 82
12.1. Subject Stopping Rules 82
12.2. Dose Group Stopping Rules 83
12.3. Discontinuation Criteria 83
13. EMERGENCY PROCEDURES 85
13.1. Emergency Contact 85
13.2. Emergency Identification of Investigational Products 85
14. REGULATORY CONSIDERATIONS 86
14.1. Good Clinical Practice 86
14.2. Investigator Responsibilities 86

14.3. Subject Information and Informed Consent 86
14.4. Confidentiality 87
14.5. Protocol Amendments 87
14.6. Institutional Review Board/Independent Ethics Committee Review and Approval 87
14.7. Ongoing Information for Institutional Review Board / Ethics Committee 88
14.8. Closure of the Study 88
15. DATA HANDLING AND RECORDKEEPING 89
15.1. Data/Documents 89
15.2. Data Management 89
15.3. Record Retention 89
16. QUALITY CONTROL AND QUALITY ASSURANCE 91
16.1. Study Monitoring and Source Data Verification 91
16.2. Audits and Inspections 91
17. PUBLICATIONS 92
18. REFERENCES 93
19. APPENDICES 96
APPENDIX A. THE CUTANEOUS LUPUS AREA AND SEVERITY INDEX 96
APPENDIX B. SWOLLEN AND TENDER JOINT COUNT – 44 JOINTS 97
APPENDIX C. PHYSICIAN'S GLOBAL ASSESSMENT 99
APPENDIX D. 1997 UPDATE OF THE 1982 ACR REVISED CRITERIA FOR CLASSIFICATION OF SLE 100
APPENDIX E. HYBRID SELENA SLEDAI 102
APPENDIX F. GILLIAM CLASSIFICATION 104
APPENDIX G. PERICARDIAL/PLEURITIC NUMERICAL PAIN SCALE 107
APPENDIX H. FATIGUE VAS 108
CCI [redacted]
APPENDIX K. MEDICATIONS THAT INHIBIT CYP3A4 116
APPENDIX L. HEPATITIS EXCLUSION CRITERIA 117
CCI [redacted]
APPENDIX O. SLICC/ACR SLE DAMAGE INDEX 123

APPENDIX P. BRITISH ISLE LUPUS ASSESSMENT GROUP 2004 127

CCI [redacted]

LIST OF TABLES

Table 1: Part 1 42
Table 2: Active Treatment Extension Phase 46

LIST OF FIGURES

Figure 1: Overall Study Design.....40

1. INTRODUCTION

Systemic lupus erythematosus (SLE) is a multi-organ autoimmune disease of unknown etiology that has many clinical manifestations. Almost any organ can be involved, but the most common manifestations are cutaneous, musculoskeletal and renal (Petri, 2006). Systemic lupus erythematosus typically affects young women of childbearing potential between the ages of 15 to 44. The prevalence of SLE is 300,000 patients in the United States and 4 million patients worldwide, with an annual incidence of 15,000 in the United States alone.

The pathogenesis of SLE likely involves an array of components associated with both genetic and environmental factors. Disease susceptibility is influenced by genes related to immune response and the major histocompatibility complex class I and II genes. Additional susceptibility stems from interactions between the hormonal environment and the hypothalamo-pituitary-adrenal axis. In addition, the development of SLE is associated with a defective immune response which affects apoptotic cell clearance and immune complexes. The loss of immune tolerance, excess T cell help, defective B cell suppression, and the shifting of T helper 1 (Th1) to Th2 and Th17 immune responses leads to B cell hyperactivity and the production of pathogenic antibodies. External factors such as chemicals, drugs, ultraviolet light, diet and viruses also contribute to the onset of disease (Mok, 2003).

As SLE is a waxing and waning disease, it is often controlled with NSAIDs or low potency immunosuppression drugs (antimalarials and low dose corticosteroids) for milder symptomology (musculoskeletal manifestation, cutaneous manifestation and serositis). More prolonged and potent use of corticosteroids, as well as non-biologic disease modifying anti-rheumatic drugs (DMARDs), are standard treatments which are also available to treat those patients who exhibit major organ involvement. In conjunction with standard therapy, biological DMARD therapies exist to augment treatment for those patients with more extensive disease. Belimumab, a monoclonal antibody and B-lymphocyte stimulator-specific inhibitor, has been approved for use in conjunction with corticosteroids and other standard therapies for autoantibody-positive SLE. In addition, Rituximab, a B-cell depleter, is often used off-label as rescue medication for patients unresponsive to standard treatment.

CC-220 is an orally available immunomodulatory drug having multiple effects on cells of the immune system, including B cells, T cells, and innate immune cells of the myeloid lineage. CC-220 is being developed for the treatment of inflammatory or autoimmune-mediated diseases such as SLE. CC-220 binds directly to cereblon (CRBN), a component of the Cullin4A-Ring E3 ubiquitin ligase cereblon complex ($CRL4^{CRBN}$), thus resulting in modulation of the ubiquitination of particular protein substrates. Lenalidomide, which is structurally similar to CC-220, is also known to bind to CRBN and modulate the ubiquitination of proteins (Ito, 2010; Lopez-Girona, 2012; Zhu, 2011), and was shown to have clinical efficacy in CLE patients in two open label studies (Braunstein, 2012; Cortes-Hernandez, 2012).

Two putative CRBN substrates reduced by CC-220 treatment in immune cells are: Ikaros, encoded by the gene IKZF1 and Aiolos, encoded by the gene Ikaros family Zinc Finger 3 (IKZF3). Ikaros and Aiolos are members of the Ikaros family of transcription factors that regulate hematopoiesis and immunity (John, 2011). While both Ikaros and Aiolos are required for B cell development (Ferreiros-Vidal, 2013; Kikuchi, 2009), Aiolos is especially important for the differentiation of long-lived antibody-secreting plasma cells (Cortes, 2004). In T cells, Aiolos is required for Th17 cell differentiation through a mechanism that involves repression of IL-2

gene transcription (Quintana, 2012). Ikaros is also responsible for repressing IL-2 gene transcription in T cells as part of the mechanism of T cell anergy (Bandyopadhyay, 2007). Both Ikaros and Aiolos are implicated in the genetic predisposition for SLE, as Genome Wide Association Studies have shown that polymorphisms in the IKZF1 and IKZF3 loci are associated with an increased risk of developing this disease (Lessard, 2012; Wang, 2012). Recently, because of its involvement in the signal transducers and activators of transcription (STAT)4 and interferon (IFN) pathways in T cells and plasmacytoid dendritic cells, Ikaros has been proposed to play a critical role in the pathogenesis of SLE (Hu, 2013).

The potential for CC-220 to have a therapeutic benefit in the treatment of SLE is supported by nonclinical data showing its impact on key pathogenic processes underlying SLE. In nonclinical in vitro models, CC-220 inhibits the differentiation of B cells into antibody-secreting plasmablasts and plasma cells, which are the source of autoantibodies in SLE. CC-220 has shown potent effects on B cell differentiation and function in peripheral blood mononuclear cells (PBMCs) obtained from patients with SLE, including the inhibition of total immunoglobulin G (IgG) and immunoglobulin M (IgM) production, as well as production of anti-dsDNA and anti-phospholipid antibodies. CC-220 is also a potent antiproliferative agent in B cell-derived tumor cell lines in vitro and demonstrates antitumor activity in multiple myeloma and lymphoma tumor xenograft models in vivo. These antiproliferative effects against B cell-derived tumors are likely to represent a further manifestation of the effects against normal B cells. CC-220 has anti-inflammatory effects on the cytokine production pathways of the innate immune response. In lipopolysaccharide-stimulated PBMC from SLE patients, CC-220 reduced production of IL-1alpha, IL-1beta, IL-6, TNF-alpha, IFN-gamma, and IL-12, all of which are overexpressed in SLE patient serum (Liu, 2013). In SLE patient-derived T cell responses ex vivo, CC-220 increases production of IL-2, a homeostatic cytokine that is underexpressed in SLE serum, and reduces production of IL-17, which is overexpressed in SLE serum (Liu, 2013). Therefore, CC-220 is an agent that demonstrates a range of immunomodulatory activities, and its ability to inhibit antibody secretion and cytokine production in particular, offers the potential for therapeutic efficacy in autoimmune conditions such as SLE.

In nonclinical safety pharmacology studies, CC-220 did not cause any change in central nervous system (CNS) functions in rats or any change in cardiovascular functions or any adverse effect in respiratory functions in monkeys. In vitro, there was no significant inhibition of the hERG (human ether-à-go-go-related gene) ion channel current by CC-220.

The systemic clearance of CC-220 following intravenous (IV) administration was moderate in both rats (≈1/2 hepatic blood flow) and monkeys (≤ 1/5 hepatic blood flow). The volume of distribution was moderate to high in rats and monkeys, suggesting good tissue distribution of CC-220. Across studies, gender differences in CC-220 exposure were modest in rats and not consistently observed in monkeys. CCI [redacted] Following oral dosing to animals, CC-220 was rapidly absorbed and the median t_{max} generally ranged from 0.5 to 2.0 hours postdose. CC-220 exhibited ≥ 60% oral bioavailability in rat and 20% in monkey.

Following oral dosing of CC-220 to rats, systemic exposures of free base was slightly higher (30% to 110%) in females than in males, and increased in an approximately dose proportional manner within 30 to 300 mg/kg single dose range or 2 to 50 mg/kg/day multiple dose range without any notable accumulation. Following multiple oral dosing of CC-220 to monkeys, systemic exposure of CC-220 at steady state increased in a greater than dose proportional manner

and there was some accumulation of CC-220 observed (accumulation ratio of 1.0 to 2.6). CCI [redacted] Protein binding of CC-220 was moderate in mouse, rat, monkey, and human, but higher in female rabbit. At 300 ng/mL, the percent (%) bound values were 79.4%, 70.4%, 95.5%, 64.1%, and 74.8% in mouse, rat, female rabbit, monkey, and human plasma, respectively, and the binding was not saturable.

The extent of metabolism was variable among rat, monkey, female rabbit, and human. Eighteen metabolites CCI [redacted] were characterized across species resulting from non-enzymatic hydrolysis, multiple oxidations of the morpholino moiety, hydrolysis of the oxidative metabolites, and a combination of these pathways. Qualitatively, all metabolites formed in human hepatocytes were also formed in hepatocytes of rat or monkey, the two species used for preclinical safety testing. CYP3A4/5 was identified as responsible for the oxidative metabolism of CC-220 in human liver microsomes. The rates and routes of excretion of CC-220 in vivo in animal species, and the excretion of CC-220 or its related components into milk, have not been evaluated. As CC-220 is a substrate for CYP3A4, concomitant administration with strong inhibitors or inducers should be avoided (Appendix K).

CC-220 has moderate intrinsic permeability and was determined to be a substrate for both P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). CC-220 is a weak inhibitor of P-gp (half maximal inhibitory concentration [IC_{50}] > 50 µM) and a moderate inhibitor of BCRP (IC_{50} = 22.3 µM). Because CC-220 is projected to be administered at low doses, the gut or systemic concentrations of CC-220 are likely to be lower than the IC_{50} for inhibition of P-gp or BCRP. Therefore, CC-220 is not anticipated to cause any clinically relevant drug-drug interactions due to inhibition of these transporters.

In rats, no CC-220-related adverse effects were noted at the highest dose of 20 mg base/kg/day (no-observed-adverse-effect-level [NOAEL]) after 6 months of dosing. CC-220 mean systemic exposures of 16100 and 21900 ng•hr/mL (an area under the plasma concentration-time curve from time 0 to 24 hours [AUC_{24hr}]) in male and female rats respectively at the NOAEL were approximately 600- to 800-fold higher than the estimated steady-state (ss) AUC_{24hr} of 27 ng•hr/mL at a once daily (QD) dose of 0.6 mg, the highest intended dose to be used in current Phase 2 and future clinical studies. This ss-AUC_{24hr} at 0.6 mg CC-220 QD was estimated based on the ss-AUC_{24hr} determined in healthy subjects receiving 0.3 mg and 1 mg CC-220 QD for 28 days in the Phase 1 multiple-ascending dose (MAD) study.

In monkeys, multiple systemic effects of CC-220 observed were primarily due to its pharmacologic effects on the immune system. These changes were observed in blood and lymphatic organs (decreased peripheral blood B, T, and natural killer (NK) cells as well as monocytes, altered cellularity in the B and T cell areas, and increased/altered heterogeneous cell mixtures in lymphoid organs), gastrointestinal tract (unformed/watery stool leading to decreased body weight gain and increased magnitude of subacute/chronic inflammation in cecum/colon), eye (increased incidence of minimal mononuclear cell infiltrates in the uveal tract), and bone marrow (myeloid hyperplasia). The impact of CC-220 treatment on humoral responses (either enhancement or attenuation) to keyhole limpet hemocyanin (KLH) in monkeys was dependent on the timing of immunization in relation to the timing of CC-220 dosing. Additional CC-220-related effects in monkeys were observed in the pancreas (degranulation/atrophy in acinar cells), testes/epididymides (bilateral hypospermatogenesis [partial to complete loss of spermatogenic epithelial cells] along with increased spermatogenic epithelial cell debris in

epididymal lumen), liver (biliary epithelial hypertrophy/hyperplasia with mononuclear/mixed inflammatory cell infiltrates), lungs (increased alveolar macrophages and decreased goblet cell secretion in trachea), and salivary glands (decreased serous cell secretion in mandibular or parotid glands). Among all CC-220-related systemic effects in monkeys, only peripheral blood B cell count was differentially affected by different dose schedules with the greatest decrease noted upon QD dosing.

Overall, adverse effects of frequent unformed/watery stools and body weight loss requiring palliative care, marked decrease in peripheral blood B cells, significantly decreased cellularity in lymphoid organs and bilateral hypospermatogenesis were observed at 0.40 mg base/kg/day in the 9-month oral toxicity study in monkeys. Thus, the NOAEL in this study was 0.12 mg base/kg/day with a mean AUC_{24hr} of 77.6 ng•hr/mL, which was approximately 3-fold higher than the estimated steady state AUC_{24hr} of 27 ng•hr/mL at 0.6 mg CC-220 QD, the highest intended dose to be used in current Phase 2 and future clinical studies.

With regards to histopathologic finding in testes/epididymides in monkeys noted at 0.40 mg base/kg/day, it is not known at this time if this finding can be reversed or at what time after start of CC-220 treatment this change occurred. There were no CC-220-related findings in the reproductive organs in female monkeys treated with 0.40 mg base/kg/day up to 9 months and in male and female rats treated up to 6 months at a dose of up to 20 mg base/kg/day (CC-220 exposure of up to 21900 ng·hr/mL). At this time, the implications of this finding in monkeys for human male reproductive health and the mechanism for this toxicity are unknown. The death of one monkey at 0.75 mg base/kg/day on Day 22 of the 1-month dose schedule study was associated with CNS-related clinical signs and diffused astrogliosis. These CNS findings in a single animal were unlikely to be causally related to CC-220 based on the lack of CNS-related effects in monkeys receiving doses of up to 1, 0.75, and 0.4 mg base/kg/day for 1, 3, and 9 months, respectively.

CC-220 was not mutagenic in the Ames assay. In an in vitro clastogenicity assay, CC-220 was negative after 4 hours with metabolic activation (S9) and 20 hours without S9. However, CC-220 was positive in the in vitro clastogenicity assay after a 4-hour treatment without S9. Further in vivo genetic toxicity testing with CC-220 in rats at the maximum tolerated dose for 3 days did not cause an increase in bone marrow micronucleus formation or any deoxyribonucleic acid (DNA) damage in the liver (Comet assay). These negative endpoints in vivo genotoxicity assays generated the weight of evidence that is considered sufficient to demonstrate a lack of significant genotoxicity risk with CC-220 in humans.

In a dose-range finding embryofetal development toxicity study in pregnant rabbits, CC-220 related developmental toxicities (decreased mean fetal body weight, increased incidences of small thymus and fused sternebrae) were observed primarily at 50 mg base/kg/day. However, CC-220 belongs to a class of drugs that is teratogenic. In light of this, detailed pregnancy avoidance/mitigation strategies have been incorporated into the protocol (Section 4.2.7).

As of 01 May 2015, 2 clinical trials have been completed in 129 healthy subjects over the dose range of 0.03 to 6 mg. Study CC-220-CP-001 was a randomized, double-blind, placebo-controlled, single ascending-dose (SAD) Phase 1 study to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of a single oral dose of CC-220 in healthy subjects. Study CC-220-CP-002, was a 3-part, multiple-ascending dose (MAD) study to evaluate

the safety, tolerability, PK, and PD of multiple doses of CC-220 and to evaluate the relative bioavailability of a formulated CC-220 capsule in healthy subjects.

Following oral administration of CC-220, systemic exposure increased in a dose-proportional manner. The median time to reach maximum observed plasma concentration (Cmax) was CCI , and steady-state was reached CCI after daily dosing. Drug accumulated in plasma after multiple daily dosing with exposure ratios CCI CCI Coadministration with a high-fat meal did not change the overall exposure when CC-220 was administered as a single dose.

CC-220 did not show significant renal elimination of unchanged drug CCI The terminal elimination half-life (t1/2) of CC-220 ranged from CCI . No significant differences were seen in the oral bioavailability CCI

The PD effects after single or multiple doses of CC-220 included: a reduction in intracellular Aiolos protein levels in both the CD19+ B cell and the CD3+ T cell populations at doses ≥ 0.3 mg; a reduction in the absolute number of CD19+ B cells in a largely dose-dependent manner at doses ≥ 0.3 mg; enhancement of CD3 antibody-induced production of T cell cytokines, such as IL-2 and IFN-γ; reduction of lipopolysaccharide (LPS)-induced production of cytokines such as IL-1β and TNF-α.

In both clinical pharmacology studies, there were no subjects who reported treatment-emergent adverse events (TEAEs) that were serious or that resulted in death. In both studies, changes in vital signs and electrocardiograms (ECGs) were minimal and clinically unremarkable. In Study CP-001, the most common TEAEs were diarrhea and TEAEs that were related to study procedure, ie, application site erythema related to the ECG patch. All TEAEs in Study CP-001 were mild in severity with the exception of one case of moderate urticaria and none led to discontinuation of IP. Changes in laboratory values were minimal and clinically unremarkable in Study CP-001. In Study CP-002, the most common TEAEs were rash (4 CC-220 subjects), neutropenia (4 CC-220 subjects), and upper respiratory tract infection (URTI, 2 placebo and 2 CC-220 subjects). A majority of TEAEs were mild in severity while all cases of neutropenia were severe. A total of 4 subjects reported TEAEs that led to study discontinuation (rash, white blood cells [WBC] in urine, and mydriasis). The clinically significant laboratory values included elevated liver function tests in 3 subjects (2 placebo, 1 CC-220) and neutropenia in 4 subjects (all CC-220). At CC-220 1 mg QD for 28 days, 4 of 6 subjects had dose-limiting toxicities of Grade 3 neutropenia after Day 21 and dosing with IP was discontinued. Per discontinuation of IP, neutrophil counts recovered toward normal values by Day 28.

This will be the first CC-220 study conducted in subjects with SLE.

Please refer to the Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies and adverse event profile of the IP.

This study will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

2. STUDY OBJECTIVES

2.1. Part 1

2.1.1. Primary

– To evaluate the safety and tolerability of CC-220 for subjects with SLE

2.1.2. Secondary

– To describe the pharmacokinetics (PK) of CC-220 for subjects with SLE

CCI [redacted]

2.2. Active Treatment Extension Phase

2.2.1. Primary

– To evaluate the long-term safety and tolerability of CC-220 in subjects with SLE who completed Part 1 of the core study

2.2.2. Secondary

– To evaluate the long-term efficacy of CC-220 in subjects with SLE who completed Part 1 of the core study

CCI [redacted]

3. STUDY ENDPOINTS

3.1. Part 1

3.1.1. Primary

– Safety (type, frequency, severity, and relationship of adverse events [AEs] to CC-220, laboratory, ECG, physical examination or other changes) and tolerability

3.1.2. Secondary

– Pharmacokinetics: PK of CC-220 in plasma, eg, AUC_t, $AUC\tau$, AUC_{inf}, C_{max}, C_{min}, t_{max}, $t_{1/2}$. CL/F and V_z/F will be evaluated at Day 1, Day 15, Day 29, Day 57 and Day 85/Early Termination.

CCI [redacted]

- CCI [redacted]

3.2. Active Treatment Extension Phase

3.2.1. Primary

- Safety:
  - Safety (type, frequency, severity, and relationship of adverse events [AEs] to CC-220, laboratory, ECG, physical examination or other changes) and tolerability

3.2.2. Secondary

- Efficacy:
  - Change in the Hybrid SELENA SLEDAI by ≥ 4 units by visit
  - Change from Baseline in the Hybrid SELENA SLEDAI by visit
  - Change from Baseline in Swollen and Tender Joint Count score by visit
  - Change from Baseline in CLASI Activity score by visit
  - Change from Baseline in the PGA by visit
  - Change from Baseline in the BILAG 2004 by visit
  - Change from Baseline in the Pericardial/Pleuritic Pain Scale by visit
  - Change from Baseline in Fatigue VAS by visit
  - Change from Baseline in CLASI Damage score by visit
  - Change from Baseline in SLICC/ACR SLE Damage Index by visit

CCI [redacted]

[redacted]

4. OVERALL STUDY DESIGN

4.1. Study Design

This is a pilot, Phase 2, randomized, placebo-controlled, double-blind, multicenter study to evaluate the preliminary efficacy, safety, tolerability, pharmacokinetics, pharmacodynamics and pharmacogenetics of CC-220 in SLE subjects with skin involvement.

This study will be conducted in 2 parts.

Part 1

Part 1 is a randomized, double-blind, placebo-controlled, ascending dose study to evaluate the safety and tolerability of CC-220 in SLE subjects.

Subject participation in Part 1 will consist of 3 phases:

- Pre-treatment Screening Phase: up to 42 days prior to the first dose of the investigational product (IP)
- Treatment Phase: up to 84 days
- Observation Phase: 84 day post-treatment (subjects who consent and qualify for the ATEP will NOT enter the Observational Phase and will directly enter the ATEP)

A total of approximately 40 subjects will be randomized into 4 dose groups with a 4:1 ratio of CC-220 (0.3 mg every other day [QOD], 0.3 mg everyday [QD], 0.6 mg and 0.3 mg on alternating days and 0.6 mg QD) or matching placebo (8 subjects in the CC-220 arm and 2 subjects in the placebo arm for each dose group) using an Interactive Voice Response System (IVRS). Subjects will be randomized into the first two dose groups of 0.3 mg QOD and 0.3 mg QD in parallel. Following confirmation of safety of the first two dose groups, remaining subjects will then be randomized into the 0.6 mg and 0.3 mg on alternating days and 0.6 mg QD dose groups in a sequential, dose-ascending manner (first the 0.6 mg and 0.3 mg on alternating days dose group followed by the 0.6 mg QD dose group). The Treatment Phase will be up to 84 days in duration for all dose groups. Subjects who discontinue IP early and all subjects who complete the 84 day treatment phase (who do not consent to enroll into the ATEP) will enter into the Observational Follow-up Phase for an 84 day period. In all cases of early termination from the study, subjects will be encouraged to complete an Early Termination Visit. See Figure 1 for graphical representation of the Part 1 dosing administration schedule.

All subjects will be allowed to remain on stable doses of hydroxychloroquine, chloroquine, and/or quinacrine for ≥ 4 weeks prior to their baseline visit and throughout the study. No additional systemic immunosuppressives will be permitted. In addition, as needed (PRN) treatment with systemic anti-pruritics and/or systemic analgesics will be permitted; subjects must stop using all systemic anti-pruritics 48 hours prior to all study visits and systemic analgesics 12 hours prior to all study visits. Oral non-steroidal anti-inflammatory drugs (NSAIDs) may be used, but must be stopped 12 hours prior to all study visits. Use of oral corticosteroids will be permitted only at doses of 10 mg or less per day and must be maintained at a stable dose during study participation. Inhaled corticosteroids for use in a disease other than lupus, eg, asthma, will be allowed. No IV (intravenous) or IM (intramuscular) corticosteroids will be permitted during

the study. No other topical (with the exception of potency class 6 and 7 topicals only), local or systemic treatments for dermatological manifestations of SLE will be permitted.

Following completion of the first 28 days of the treatment phase by at least 8 subjects in Dose Group 1 (0.3 mg QOD) and 8 subjects in Dose Group 2 (0.3 QD), an assessment of safety and tolerability will be conducted. If Dose Groups 1 and 2 are deemed to have acceptable safety and tolerability, subjects will continue to receive investigational product for up to 84 days and enrollment of subjects into Dose Group 3 (0.6 mg and 0.3 mg on alternating days) will be initiated. Following completion of the first 28 days of the treatment phase by at least 8 subjects in Dose Group 3 (0.6 mg and 0.3 mg on alternating days), an assessment of safety and tolerability will be conducted. If Dose Group 3 is deemed to have acceptable safety and tolerability, subjects will continue to receive investigational product for up to 84 days and enrollment of subjects into Dose Group 4 (0.6 mg QD) will be initiated. Following completion of the first 28 days of the treatment phase by at least 8 subjects in Dose Group 4 (0.6 mg QD), an assessment of safety and tolerability will be conducted. If Dose Group 4 is deemed to have acceptable safety and tolerability, subjects will continue to receive investigational product for up to 84 days.

Subjects will remain on their assigned treatment for up to 84 days. In the event a subject experiences clinically significant IP-related adverse events (AEs), a dose interruption for up to 14 days will be permitted (see Section 12.1). If a subject is unable to remain on their assigned dose, he/she may reduce their dose to the next lowest dosing regimen. Dose reductions will occur as follows:

- Subjects on 0.6 mg QD will reduce their dose to 0.6 mg/0.3 mg on alternating days
- Subjects on 0.6 mg/0.3 mg on alternating days will reduce their dose to 0.3 mg QD
- Subjects on 0.3 mg QD will reduce their dose to 0.3 mg QOD
- Subjects on 0.3 mg QOD will reduce their dose to placebo

A subject will only be permitted to reduce their dose one time during the study. The decision to modify IP dosing will be based on the rules provided in Section 12.1. The sponsor should be notified of the intent to dose reduce prior to a change in dosing.

Subjects who discontinue from the study prior to completing 28 days of treatment may be replaced (for up to a total of 10 subjects for Part 1) at the discretion of the sponsor.

Active Treatment Extension Phase

The Active Treatment Extension Phase (ATEP) is an extension of the core CC-220-SLE-001 study to evaluate the long-term efficacy and safety/tolerability of CC-220 in SLE subjects who completed Part 1 of the core study.

Subjects who complete the Treatment Phase of Part 1 of the core study (CC-220-SLE-001) will be eligible to receive CC-220 in the ATEP for up to 2 years. All subjects who participate in the ATEP will receive the same active treatment they received during their participation in Part 1 with the exception of those on placebo or 0.3 mg QOD (see below for information on dosing for these subjects).

Subjects who complete the Treatment Phase of Part 1 of the core study will immediately be eligible to enter this phase of the study and should be enrolled immediately to avoid dose interruption. In the event the ATEP has not been implemented by subjects' study sites at the time they have completed the treatment phase for Part 1, subjects will enter the Observation Phase of the core study and be eligible to enroll in the ATEP upon implementation of ATEP amendment. There were no time restrictions on how long subjects can be off CC-220 prior to entering the ATEP as long as they completed treatment in Part 1 of the core study, but with the implementation of Protocol Amendment 5, enrollment into the ATEP is now closed. Subjects who terminate the treatment phase of Part 1 early will not be eligible for entry into the ATEP.

Subject participation consists of two phases:

- Active Treatment Extension Phase: Up to 2 years
- Observational Follow-up Phase: 28 days

Subjects receiving CC-220 0.3 mg QOD or CC-220 0.3 mg QD during their participation in the core study will be assigned to receive CC-220 0.3 mg QD during the ATEP. Subjects receiving CC-220 0.6 mg/0.3 mg on alternating days during their participation in the core study will remain on the same assigned dose during the ATEP. Subjects receiving CC-220 0.6 mg QD during their participation in the core study were originally permitted to enter the ATEP on the same dose. However, based on data that has become available for Part 1 (see Section 4.2.3), any subject originally enrolled in the ATEP on the 0.6 mg QD dose should be dose reduced to the 0.6 mg/0.3 mg on alternating days dose upon implementation of Protocol Amendment 5.

Subjects receiving placebo during their participation in the core study (Part 1) will receive the CC-220 dose given to those on active drug in their respective cohort. For example, if a subject was taking placebo in Dose Group 3 of Part 1, he or she would receive CC-220 0.6 mg/0.3 mg on alternating days during the ATEP. However, based on data that has become available for Part 1 (see Section 4.2.3), any subject who was on placebo in the 0.6 mg QD cohort for Part 1 and originally entered the ATEP on 0.6 mg QD should be dose reduced to 0.6/0.3 mg QD on alternating days upon implementation of Protocol Amendment 5.

For subjects who are eligible to roll directly into the ATEP, Week 12 (Visit 10) of Part 1 may be on the same day as Visit 1 of the ATEP. All Visit 10 (Part 1) and Visit 1 (ATEP) procedures must be conducted as outlined in Table 1 and Table 2. Please note that subjects rolling directly into the ATEP who have both Week 12 (Visit 10) of Part 1 and Visit 1 of the ATEP on the same day, will only undergo a subset of assessments for Visit 1 of the ATEP (indicated in Table 2). If the subject remains eligible for entry into the ATEP following Visit 1 assessments, drug will be dispensed and the subject will begin the ATEP. Subjects entering the ATEP who cannot hold their Week 12 (Visit 10) of Part 1 and Visit 1 of the ATEP on the same day, can hold their Visit 1 of the ATEP at any time after their sites has received IRB approval. **However, once 14 days have elapsed since a subject has had their Week 12 (Visit 10) of Part 1, they must undergo the ATEP Screening Visit and all assessments listed for Visit 1 of the ATEP in Table 2 if they wish to enter the ATEP. As long as a subject comes in for their Visit 1 ATEP within 14 days after their Part 1 Week 12 (Visit 10) they will only need to complete the subset of assessments identified under footnote b of Table 2.**

All subjects will be allowed to remain on stable doses of hydroxychloroquine, chloroquine, and/or quinacrine for ≥ 4 weeks prior to their baseline visit and throughout the study. Subjects on

antimalarials will be permitted to modify or stop their treatment at any time during the ATEP. Methotrexate (7.5 mg – 25 mg per week), leflunomide (maintenance dosing must not exceed 20 mg daily) or sulfasalazine (dosing not to exceed 3 g daily) will be permitted, although no other additional systemic immunosuppressives will be permitted. In addition, PRN treatment with systemic anti-pruritics and/or systemic analgesics will be permitted. However, subjects must stop using all systemic anti-pruritics 48 hours prior to all study visits and systemic analgesics 12 hours prior to all study visits. Oral NSAIDs may be used, but must be stopped 12 hours prior to all study visits. Use of oral corticosteroids will be permitted only at doses of 10 mg or less per day and must be maintained at a stable dose during study participation. Inhaled corticosteroids for use in a disease other than lupus, eg, asthma, will be allowed. No IV or IM corticosteroids will be permitted during the study. No other topical (with the exception of potency class 6 and 7 topicals only), local or systemic treatments for dermatological manifestations of SLE will be permitted.

Thromboprophylaxis with low dose aspirin, low molecular weight heparin or other equivalent antithrombotic or anticoagulant is required unless the investigator determines that, based on the totality of the subjects' risk factors for thrombosis, thromboprophylaxis is not required or is contraindicated.

If any additional prophylaxis is needed, it should be based on the local standard of care and the investigator's best judgement after careful consideration of the benefit versus the potential risk for the individual subject.

Subjects will remain on their assigned treatment for up to 2 years. In the event a subject experiences clinically significant IP-related AEs, a dose interruption for up to 14 days will be permitted (see Section 12.1). If a subject is unable to remain on their assigned dose, he/she may reduce their dose to the next lowest dosing regimen. Dose reductions will occur as follows:

- Subjects on 0.6 mg QD will reduce their dose to 0.6 mg/0.3 mg on alternating days
- Subjects on 0.6 mg/0.3 mg on alternating days will reduce their dose to 0.3 mg QD
- Subjects on 0.3 mg QD will be terminated from the study

A subject will only be permitted to reduce their dose one time during the study (subjects who originally came into the ATEP on 0.6 mg QD and dose reduce to 0.6/0.3 mg QD on alternating days upon implementation of Protocol Amendment 5 will be eligible for one additional dose reduction in the ATEP). The decision to modify IP dosing will be based on the rules provided in Section 12.1. The sponsor should be notified of the intent to dose reduce prior to a change in dosing.

Subjects will have regularly scheduled visits to assess IP activity and safety. Required assessments will be completed as depicted in Table 2.

Upon completion of, or discontinuation from the ATEP, all subjects (including premature discontinuations) will enter a 28 day Observational Follow-up Phase. Subjects who discontinue IP early should complete an Early Termination Visit.

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and applicable regulatory requirements.

4.2. Study Design Rationale

4.2.1. Duration of Treatment

The length of study participation for each subject in Part 1 is 210 days (Up to a 42-day Screening Phase, 84-day Treatment Phase and an 84-day Observational Follow-Up Phase). The length of study participation for each subject in the ATEP is up to 2 years and 1 month (up to a 2-year ATEP and a 4-week post-treatment Observational Follow-Up Phase). Subjects who participate in both Part 1 and the ATEP will participate in the study for a total of approximately 2 years and 6 months.

4.2.2. Study Population

The study population will consist of male and female subjects 18 years of age and older at the time of signing the ICD.

Subjects in Part 1 are required to have:

- An established diagnosis of SLE as defined by the 1997 Update of the 1982 ACR Revised Criteria for Classification of SLE at Screening (Appendix D) and a minimum Hybrid SELENA SLEDAI score of ≥ 4 points.

Subjects in the Active Treatment Extension Phase are required to have:

- Completed the CC-220-SLE-001 core study (Part 1).

4.2.3. Dose and Dose Interval

The primary objective of this study is to determine the safety and tolerability of CC-220 in subjects while on a stable standard of care for the treatment of SLE over a 12-week period. To achieve this objective, 0.3 mg QD and 0.6 mg QD were selected based upon available data to support the safe administration of these doses in the SLE population and the likelihood that these doses will demonstrate safety and efficacy in a 12-week study.

The nonclinical PK, metabolism, toxicity and clinical pharmacology studies conducted to date were used to characterize the toxicity profile of CC-220 and to provide information with regard to the planned doses in this study. Specifically, the 28-day monkey study and the Phase 1 clinical pharmacology CC-220-CP-001 and CC-220-CP-002 studies (described in the Investigator's Brochure [IB]) with regard to target organ toxicity, NOAEL, and safety margins support the planned doses and regimens in this 12-week study.

The 0.3 mg QOD was selected as the lowest dose, based upon the demonstrated effect on Aiolos protein levels in lymphocytes, the reduction in peripheral B cells after a single 0.3 mg dose, and the sustained increase in T cell IL-2 production observed with the 0.3 mg every 3 days (Q3D) dose. The dose of 0.3 mg QD is supported by the Phase 1 data that showed that 0.3 mg QD x 28-day dose was well tolerated in healthy subjects and exhibited sustained effects on multiple PD parameters. The 0.3 mg QD dose x 28 days demonstrated a significant reduction in CD19+ B cells, and a reduction in CD3+ T cells.

The highest planned dose of 0.6 mg QD was based upon data which is lower than the dose (1 mg QD dosed for 28 days) at which the dose-limiting toxicity of Grade 3 neutropenia was observed in healthy subjects. A dose of 0.6 mg QD was selected to better understand the safety/PD profile

of CC-220 in SLE subjects. Since 0.6 mg QD was not tested in healthy subjects, the cohort of 0.6 mg QD commenced only after the 0.3 mg QD dose was deemed to be safe and well tolerated. Because grade 3 neutropenia was observed at the 1 mg QD dose, neutrophil counts were closely monitored, and dose modification criteria were pre-specified in the protocol (Section 12). Based on PK/PD modeling, higher pharmacological effects were anticipated from the 0.6 mg QD over the 0.3 mg QD dose. Therefore, based upon the tolerated dose of 0.3 mg QD x 28 days, and the PK/PD modeling, the 0.3 mg and 0.6 mg QD doses were selected for this study.

Data from Part 1 of CC-220-SLE-001 have revealed that there was a significant increase in plasma cells and a trend for increasing CD4 and CD8 T cells in patients receiving the 0.6 mg QD dose. Additionally, Grade 3 neutropenia and dermatitis were observed with the 0.6 mg QD dose. As a result, any subject enrolled in the ATEP on the 0.6 mg QD dose should be dose reduced to 0.6 mg/0.3 mg on alternating days. Subjects in the ATEP taking 0.3 mg QD and 0.6/0.3 mg QD on alternating days should continue their IP as these doses were shown to reduce key SLE cytokines with a less pronounced side effect profile.

Please refer to the Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies and adverse event profile of CC-220.

4.2.4. Blinding

Part 1 of this study are randomized, double-blind and placebo-controlled to reduce the potential for bias and validate the results observed.

4.2.5. Concomitant Medications

All subjects will be allowed to remain on stable doses of hydroxychloroquine, chloroquine, and/or quinacrine for ≥ 4 weeks prior to their baseline visit and throughout the study. In addition, while subjects are enrolled in the ATEP, they will be permitted to modify or stop their antimalarial treatment at any time. During the placebo-controlled phase, no additional systemic immunosuppressives will be permitted. During the ATEP, methotrexate, leflunomide or sulfasalazine will be permitted if clinically indicated, although no other additional systemic immunosuppressives will be permitted. In addition, as needed PRN treatment with systemic anti-pruritics and/or systemic analgesics will be permitted, however, subjects must stop using all systemic anti-pruritics 48 hours prior to all study visits and systemic analgesics 12 hours prior to all study visits. Oral NSAIDs may be used, but must be stopped 12 hours prior to all study visits. Use of corticosteroids will be permitted only at doses of 10 mg or less per day, and the dose must remain stable for the duration of the subject's participation in the study. No IV or IM corticosteroids will be permitted during the study. Inhaled corticosteroids for use in a disease other than lupus, eg, asthma, will be allowed. Only use of topical steroids that fall into potency classes 6 and 7 will be permitted during the study. No other topical, local or systemic treatments for dermatological manifestations of SLE will be permitted.

Thromboprophylaxis with low dose aspirin, low molecular weight heparin or other equivalent antithrombotic or anticoagulant is required unless the investigator determines that, based on the totality of the subjects' risk factors for thrombosis, thromboprophylaxis is not required or is contraindicated.

Medication doses and treatment regimens should remain generally stable throughout the course of the study.

4.2.6. Efficacy

The efficacy assessments included in this proof-of-concept (PoC) protocol target some of the key clinical manifestations, eg, skin, joint, etc, of SLE and may provide information on the potential of CC-220 to treat them. These evaluations, which include the Hybrid SELENA SLEDAI, CLASI, etc, are accepted, well-known assessments that are frequently used in SLE clinical studies. The potential for use of these scales, or a composite of these scales, to be included in future studies will also be explored.

4.2.7. Safety

General and specific safety precautions such as the use of clinical investigators highly experienced in this indication, frequent study visits, careful ongoing monitoring of clinical (including physical and eye examinations), ECGs and laboratory findings by the sponsor, have been implemented in this protocol.

CC-220 is a thalidomide analog and new immunomodulatory drug. Suppression of bone marrow-derived blood cell-forming elements (with or without infection) is the primary toxicity finding for immunomodulatory compounds. Therefore, safety monitoring will include repeated hematology (white blood cell [WBC] count with differential) and platelet counts. In addition, routine chemistry (total protein, albumin, calcium, phosphorous, glucose, uric acid, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/ serum glutamic-pyruvic transamine (SGPT), sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, estimated glomerular filtration rate [eGFR] in mL/min using the Modification of Diet in Renal Disease formula (MDRD eGFR – as calculated and reported by the central laboratory), protein creatinine ratio, lactate dehydrogenase (LDH), and magnesium), and urinalyses (to measure urine sediment, albumin and protein), will be assessed at frequent intervals.

CC-220 has been shown to impact B-cell differentiation, including inhibition of IgG and IgM production in PBMCs obtained from patients with SLE. Quantification of total IgG, IgM and immunoglobulin A (IgA) will be assessed in this study.

Due to the minimal to mild degranulation/atrophy in pancreatic acinar cells observed in the monkeys treated for 3 months, (which were most likely secondary to animals' clinical condition) serum level for micronutrients (eg, apolipoproteins, total cholesterol, and lipid-soluble vitamins [A,D,E,K]) in addition to lipase and amylase will also be monitored throughout the study.

To monitor for the potential attenuation of vaccine effectiveness due to CC-220, tetanus toxoid, pneumococcal, and influenza titers will be monitored during the course of the study.

To monitor for possible immune activation, high sensitivity C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and fibrinogen will be measured during the study.

Several pre-dose electrocardiographic (12-lead) recordings will be obtained throughout the study and assessed by a central (cardiologist) reader. The cardiologist will interpret all ECGs with relevance to PR interval, QRS duration, heart rate and R-R interval, QT and QTc.

Due to the potential immunomodulatory effects of CC-220, subjects will be screened (and excluded) for evidence of active viral hepatitis infections (hepatitis B and C) utilizing the screening hepatitis panel.

During toxicology testing there were uveal tract findings. As a result, ophthalmological examinations conducted by a qualified ophthalmologist will be required. Testing will include visual acuity and slit lamp exams with fluorescein staining following pupillary dilation. In addition, toxicology testing yielded testicular findings. Consequently, testosterone, FSH and LH will be monitored for all male subjects randomized into the study.

Study personnel are expected to be vigilant with respect to serious or opportunistic infections.

In order to reduce the potential for clinically significant immunosuppression anticipated by the use of concomitant therapy with CC-220 and high-dose corticosteroids, subjects will be permitted to use no more than 10 mg/day (or equivalent) of oral prednisone (or its equivalent).

Due to the elevated risk of thromboembolic events associated with lupus and CC-220, thromboprophylaxis with low dose aspirin, low molecular weight heparin or other equivalent antithrombotic or anticoagulant is required unless the investigator determines that, based on the totality of the subjects' risk factors for thrombosis, thromboprophylaxis is not required or is contraindicated.

If any additional prophylaxis is needed, it should be based on the local standard of care and the investigator's best judgement after careful consideration of the benefit versus the potential risk for the individual subject.

Although embryofetal developmental studies in non-clinical species with CC-220 have not yet been conducted, CC-220 belongs to a class of drugs that is teratogenic. In light of this, detailed pregnancy avoidance/mitigation strategies have been incorporated into the protocol. These include:

- Regular medically supervised pregnancy testing for FCBP. Investigational product will not be dispensed until negative pregnancy test results have been confirmed by the Investigator.
- Specific birth control requirements for all subjects. At each visit, the Investigator must confirm with FCBP that she is continuing to use two reliable methods of birth control. Males (including those who have had a vasectomy) must use barrier contraception (condoms) when engaging in sexual activity with a FCBP.
- Counseling regarding pregnancy/breastfeeding precautions, potential risks of fetal exposure, handling of IP and blood/sperm/semen donations will be conducted at a minimum of every 28 days.
- Pregnancy testing and counseling if a subject misses her menstrual period, or if her pregnancy test or menstrual bleeding is abnormal. Investigational product will be discontinued during this evaluation.
- Immediate discontinuation of CC-220 if pregnancy or a positive pregnancy test occurs in a subject who is a FCBP. If pregnancy or a positive pregnancy test occurs in the partner of a male subject, the Investigator must be notified immediately.

- No more than a 28-day supply of IP may be dispensed at a time.

4.2.7.1. Internal Celgene Monitoring at the Study Level

All safety measures, which are assessed at each study visit by the collection of adverse events and changes in concomitant medications, monitoring of vital signs and laboratory results collected from the scheduled visits, will be reviewed on an ongoing basis at the subject level by the internal Celgene study team. All serious adverse events (SAEs) will also be collected, reviewed, analyzed and reported as required by local regulations.

4.2.7.2. Internal Celgene Safety Monitoring of CC-220 at the Compound Level – Role of the Safety Management Team

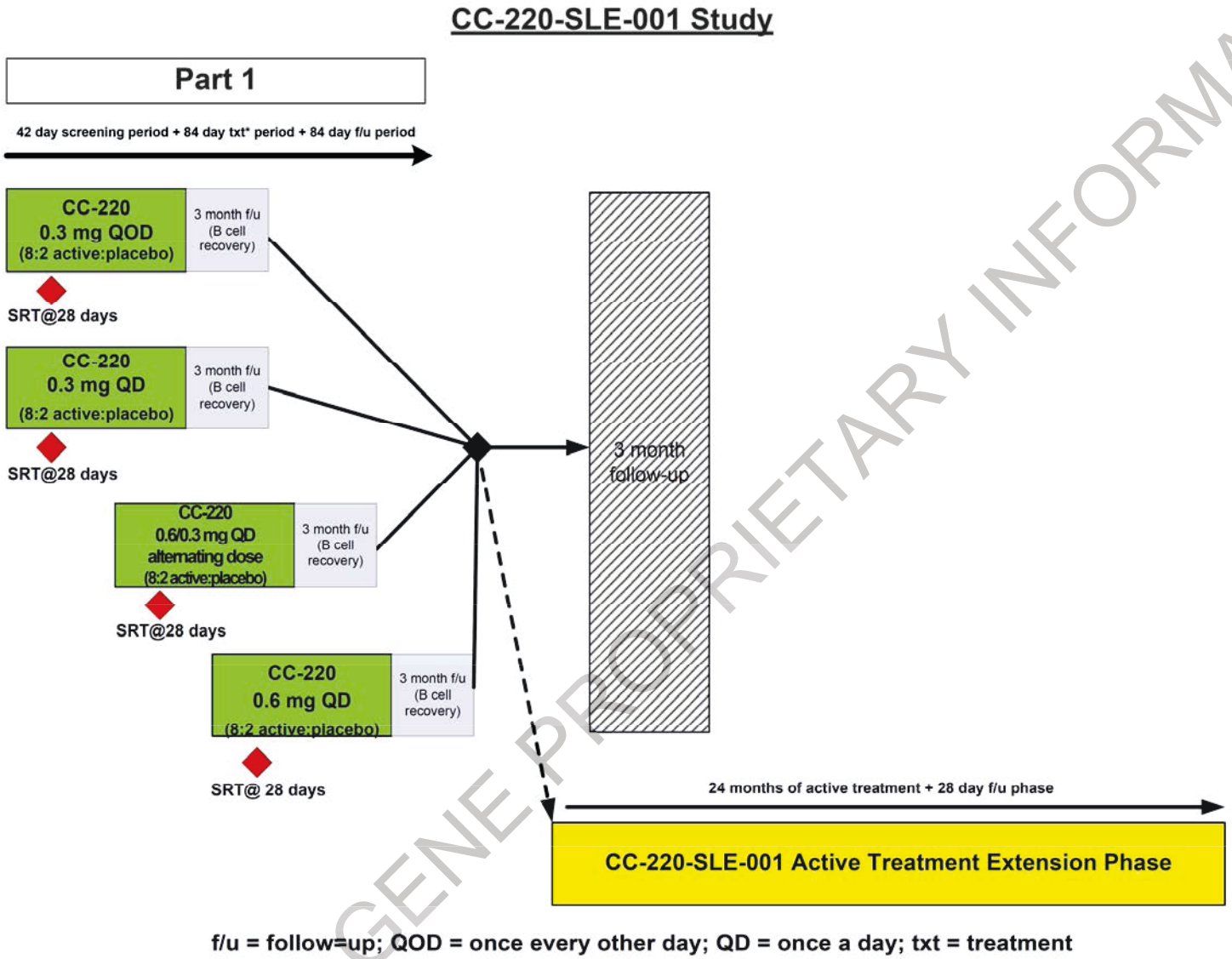
In addition to daily safety monitoring conducted by Investigators, site study personnel, and by the Celgene study team; cumulative and interval AEs, SAEs, discontinuations and laboratory findings will be reviewed by a Safety Management Team (SMT) internally at Celgene. The review follows the Council for International Organizations for Medical Sciences, Working Group VI (CIOMS VI) recommendation. The SMT is comprised of lead representatives from multiple Celgene functions engaged in the CC-220 development program.

4.2.8. Pharmacokinetic CCI Markers

Pharmacokinetic measures are incorporated into the study to assess the extent of exposure and to explore the relationship between IP exposure and response.

CCI

Figure 1: Overall Study Design



4.3. Study Duration

The study duration for each subject in Part 1 is 210 days (Up to a 42-day Screening Phase, 84-day Treatment Phase and an 84-day Observational Follow-Up Phase). The length of study participation for each subject in the ATEP is up to 2 years and 1 month (up to a 2-year ATEP and a 28-day post-treatment Observational Follow-Up Phase). Subjects who participate in both Part 1 and the ATEP will participate in the study for a total of approximately 2 years and 6 months.

4.4. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the study, 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 pre-specified in the protocol and/or the Statistical Analysis Plan, whichever is the later date.

5. TABLE OF EVENTS

Table 1: Part 1

Visit(s) ±1 Day – for all visits	Pre-treatment Phase	Treatment Phase							Observational Follow-Up Phase[e]	
	1 Screening	2 Baseline	3	4	5	6	7-9	10 Final Treatment Visit / Early Termination Visit	11	12
Day(s)	-42	1	8	15	22	29	43, 57, 71	85	Day 113 4 weeks Post-treatment	Day 169 12 weeks Post-treatment
Study Entry										
Informed Consent	X	-	-	-	-	-	-	-	-	-
Intensive PK Sub-study Consent	X	-	-	-	-	-	-	-	-	-
Inclusion/Exclusion Criteria	X	X	-	-	-	-	-	-	-	-
Medical History	X	-	-	-	-	-	-	-	-	-
Safety Assessments										
Ophthalmology Exams	X	-	-	-	-	-	-	X	-	-
Complete Physical Exam	X	-	-	-	-	-	-	X	-	X
Targeted Physical Exam	-	X	-	-	X	-	Day 57	-	X	-
Vital Signs	X	X	X	X	X	X	X	X	X	X
Hepatitis B and C	X	-	-	-	-	-	-	-	-	-
Hematology, Chemistry and Urinalysis	X	X	-	X	-	X	X	X	X	X
IgA, IgM and IgG	X	-	-	-	-	-	Day 57	X	-	-
Inflammation Panel	-	X	X	X	-	X	Day 57	X	X	-
Serum β-HCG Pregnancy Test[a]	X	X	-	-	-	X	Day 57	X	-	X

Table 1: Part 1 (Continued)

Visit(s) ±1 Day – for all visits	Pre-treatment Phase	Treatment Phase							Observational Follow-Up Phase[e]	
	1 Screening	2 Baseline	3	4	5	6	7-9	10 Final Treatment Visit / Early Termination Visit	11	12
Day(s)	**-42**	**1**	**8**	**15**	**22**	**29**	**43, 57, 71**	**85**	**Day 113 4 weeks Post-treatment**	**Day 169 12 weeks Post-treatment**
Urine Pregnancy Test[b]	-	X	X	X	X	X	X	-	X	-
Tetanus Toxoid Titer[f]	-	X	-	-	-	-	-	X	-	X
Apolipoproteins, total cholesterol and lipid-soluble vitamins A, D, E and K	-	X	-	-	-	X	Day 57	X	X	-
PT, INR and PTT	-	X	-	-	-	-	Day 43	X	-	X
12-Lead ECG	X	X	X	-	-	-	Day 43	X	X	-
Adverse Events	X	X	X	X	X	X	X	X	X	X
Prior/Concomitant Meds and Procedures	X	X	X	X	X	X	X	X	X	X
Testosterone, FSH and LH[c]	-	X	-	-	-	-	-	X	-	-
Celgene Pregnancy Prevention Counseling Program (CPPCP)	X	X	X	X	X	X	X	X	X	-
Efficacy Assessments										
CLASI Activity	X	X	-	X	-	X	Day 57	X	X	X
CLASI Damage	-	X	-	-	-	-	-	X	-	-
Hybrid SELENA SLEDAI	X	X	-	X	-	X	Day 57	X	X	X
Swollen and Tender Joint Count	-	X	-	X	-	X	Day 57	X	X	X
PGA	-	X	-	X	-	X	Day 57	X	X	X
Pericardial/Pleuritic Pain Scale	X	X	-	X	-	X	Day 57	X	X	X
SLICC/ACR SLE Damage Index	-	X	-	-	-	-	-	X	-	-

Table 1: Part 1 (Continued)

Visit(s) ±1 Day – for all visits	Pre-treatment Phase	Treatment Phase							Observational Follow-Up Phase[e]	
	1 Screening	2 Baseline	3	4	5	6	7-9	10 Final Treatment Visit / Early Termination Visit	11	12
Day(s)	-42	1	8	15	22	29	43, 57, 71	85	Day 113 4 weeks Post-treatment	Day 169 12 weeks Post-treatment
PK/CCI Assessments										
Sparse PK Blood Collection	-	-	-	X	-	X	Day 57	X	-	-
Intensive PK Blood Collection[d]	-	X	-	X	-	X	Day 57	X	-	-
CCI										
Investigational Product										
Dispense IP	-	X	-	X	-	X	X	X	-	-
IP Compliance	-	-	X	X	X	X	X	X	-	-

HCG = beta human chorionic gonadotropin; ECG = electrocardiogram; IgG = immunoglobulin G; IgM = immunoglobulin M; IgA = immunoglobulin A; IP = investigational product; PK = pharmacokinetics; VAS = visual analog scale; PPRMP= Pregnancy Prevention Risk Management Plans; PT=prothrombin time; INR=internationalized normalized ratio; PTT=partial thromboplastin time; HBsAg=Hepatitis B surface antigen; CLASI=Cutaneous Lupus Area and Severity Index; PGA=physician global assessment; SLEDAI= Systemic Lupus Erythematosus Disease Activity Index; CCI FSH=follicle-stimulating hormone; LH=luteinizing hormone; IRB=institutional review board.

[a] **FCBP are required to have 2 negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting IP. The first pregnancy test must be performed within 10 to 14 days prior to the start of IP and the second test must be performed within 24 hours of starting IP.** The subject may not receive IP until the Investigator has verified that the results of these pregnancy tests are negative. FCBP with 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 Day 113 and Day 169 following IP discontinuation (if urine pregnancy test is positive on Day 113, a serum pregnancy test must be conducted to confirm result). If menstrual cycles are irregular or do not occur, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at treatment discontinuation and at 14 and 28 days following treatment discontinuation.

[b] 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 and within 28 days of discontinuing investigational product.

[c] Collection of these analytes must occur **at the same time of day (± 1 hour)** at the Baseline (Visit 2) and Day 85 (End of Treatment or Early Termination Visit) **for males only**. For example, if collected at the Baseline Visit at 9 AM, the Final Treatment/Early Termination Visit sample must be collected between 8 and 10 AM.

[d] On Day 1 and Day 29 PK blood samples will be collected at pre-dose (Time=0 hours), 1, 2, 3, 4, between 6 and 8 hours and 24 hours (±5 hours) after administration of IP.

[e] Subjects who discontinue treatment early should enter into the Observational Follow-up Phase. Subjects who elect to enter the ATEP (at sites which have IRB approval for the ATEP) will not enter the Observational Follow-Up Phase and directly enter the ATEP. Those subjects who conclude their treatment at a site which does not have IRB approval for the ATEP must enter the Observational Follow-Up Phase. Subjects who would like to enter ATEP, but whose site does not have IRB approval may enter the Observational Follow-Up Phase and then enter the ATEP once the site's IRB approves the amendment containing the ATEP.

[f] If a subject is planning to receive a primary booster dose of pneumococcal vaccine at any time during the study, a prevaccination blood sample should be obtained to measure the prevaccination titer.

Table 2: Active Treatment Extension Phase

Visit(s) ±1 Day – for all visits[h]		Year 1																Year 2												Observational Follow-Up[i]
	0 Screening	1[a] Baseline for ATEP	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27 Final Treatment Visit / Early Termination Visit	28
Week(s)	**-6**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**
Study Entry																													
Informed Consent	X	X[b]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion/Exclusion Criteria	X	X[b]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Safety Assessments																													
Ophthalmology Exams	-	X	-	-	-	-	-	-	-	X	-	-	-	-	-	X	-	-	-	-	-	X	-	-	-	-	-	X	-
Complete Physical Exam[c]	X	X	-	-	-	-	-	-	-	X	-	-	-	-	-	X	-	-	-	-	-	X	-	-	-	-	-	X	-
Targeted Physical Exam[c]	-	-	X	X	X	X	X	X	X	-	X	X	X	X	X	-	X	X	X	X	X	-	X	X	X	X	X	-	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis B and C	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hematology, Chemistry and Urinalysis[d]	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
Amylase and Lipase	-	X[b]	-	-	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	X
eGFR, protein creatinine ratio	X	X[b]	-	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
IgA, IgM and IgG	X	X	-	-	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	X
Inflammation Panel	-	X	-	-	X	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	X
Serum β-HCG Pregnancy Test[e]	X	X	-	-	X	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	X
Urine Pregnancy Test[e]	-	X[b]	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

Table 2: Active Treatment Extension Phase (Continued)

Visit(s) ±1 Day – for all visits[h]		Year 1																Year 2												Observational Follow-Up[i]
	0 Screening	1[a] Baseline for ATEP	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27 Final Treatment Visit / Early Termination Visit	28
Week(s)	**-6**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**
Tetanus toxoid, pneumococcal and influenza titers[j]	-	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-	-	-	-	X	-
Apolipoproteins, total cholesterol and lipid-soluble vitamins A, D, E and K	-	X	-	-	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-
PT, INR and PTT	-	X	-	-	X	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-
Lupus Autoantibody/Complement Panel	X	X	-	-	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-
Lupus Anti-Phospholipid Profile	-	X	-	-	-	-	-	-	-	X	-	-	-	-	-	X	-	-	-	-	-	X	-	-	-	-	-	X	-
12-Lead ECG	X	X	X	-	X	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	X
Adverse Events	X	X[b]	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
Prior/Concomitant Meds and Procedures	X	X[b]	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
Testosterone, FSH and LH[f]	-	X	-	-	-	-	-	-	-	X	-	-	-	-	-	X	-	-	-	-	-	X	-	-	-	-	-	X	-
Celgene Pregnancy Prevention Counseling Program (CPPCP)[g]	X	X[b]	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
Efficacy Assessments																													
BILAG 2004	X	X[b]	X	-	X	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	X
CLASI Activity	X	X	X	-	X	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	X

Table 2: Active Treatment Extension Phase (Continued)

Visit(s) ±1 Day – for all visits[h]	0 Screening	Year 1															Year 2												Observational Follow-Up[i]
		1[a] Baseline for ATEP	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27 Final Treatment Visit / Early Termination Visit	28
Week(s)	**-6**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**
CLASI Damage	-	X	X	-	X	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	X
Hybrid SELENA SLEDAI	X	X	X	-	X	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	X
Swollen and Tender Joint Count	-	X	X	-	X	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	X
PGA	-	X	X	-	X	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	X
Pericardial/Pleuritic Pain Scale	X	X	X	-	X	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	X
SLICC/ACR SLE Damage Index	-	X	X	-	X	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	X
CCI [redacted]																													
Fatigue VAS	-	X[b]	X	-	X	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	-
Investigational IP																													
Dispense IP	-	X[b]	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
IP Compliance	-	-	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	-

HCG = beta human chorionic gonadotropin; ECG = electrocardiogram; IgG = immunoglobulin G; IgM = immunoglobulin M; IgA = immunoglobulin A; IP = investigational product; VAS = visual analog scale; PPRMP= Pregnancy Prevention Risk Management Plans; PT=prothrombin time; INR=internationalized normalized ratio; PTT=partial thromboplastin time; CLASI=Cutaneous Lupus Area and Severity Index; PGA=physician global assessment; SLEDAI= Systemic Lupus Erythematosus Disease Activity Index; CCI FSH=follicle-stimulating hormone; LH=luteinizing hormone; BILAG=British Isles Lupus Assessment Group; CCI ; ATEP=Active Treatment Extension Phase; FCBP=females of child bearing potential; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CO2=carbon dioxide; CCI ; SLICC/ACR SLE= Systemic Lupus International Collaborating Clinics/American College of Rheumatology Systemic Lupus Erythematosus.

[a] For subjects who are rolling directly into the ATEP, Week 12 (Visit 10) of Part 1 may be conducted on the same day as Visit 1 of the ATEP. Visit 1 must be completed only after the Part 1 Week 12 (Visit 10) of the core study has been completed. In the instance that these visits occur on the same day, only a subset of assessments for Visit 1 of the ATEP will need to be conducted (see Footnote b below). Drug may be dispensed for the ATEP as long as the subject successfully completes Visit 1 of the ATEP and remains eligible for entry. See Footnote e for specific pregnancy requirements.

[b] **These are the only assessments that need to be done for Visit 1 of the ATEP for subjects who are having their Part 1 Week 12 (Visit 10) on the same day as their Visit 1 of the ATEP. Subjects who come into the site for their Visit 1 of the ATEP greater than 14 days after their Part 1 Week 12 (Visit 10) must undergo the ATEP Screening Visit and the full Visit 1 of the ATEP as listed in the table above. In the event a subject comes in for their Visit 1 ATEP within 14 days after their Part 1 Week 12 (Visit 10) they will only need to complete the subset of assessments identified with the footnote b notation.**

[c] At every visit both weight and waist circumference (measured at both the umbilicus and the level of the anterior iliac crests) will be measured to determine the subject's risk for metabolic syndrome.

[d] A full chemistry panel will be run quarterly (every 3 months). At the visits falling in between the quarterly visits, partial chemistry panels will be run. These will consist of the following labs: albumin, alkaline phosphate, ALT, AST, BUN, calcium, chloride, CO_2, creatinine, potassium, sodium, total bilirubin, total protein and glucose (non-fasting).

[e] FCBP are required to have 2 negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting IP. The first pregnancy test must be performed within 10 to 14 days prior to the start of IP and the second test must be performed within 24 hours of starting IP. The subject may not receive IP until the Investigator has verified that the results of these pregnancy tests are negative. FCBP with regular cycles must have pregnancy testing weekly (except for Week 3) for the first 28 days of study participation and then every 28 days while on study, at study discontinuation and at Week 100 following IP discontinuation (if urine pregnancy test is positive on Week 100, a serum pregnancy test must be conducted to confirm result). If menstrual cycles are irregular or do not occur, the pregnancy testing must occur weekly (except for Week 3) for the first 28 days and then every 14 days while on study, at treatment discontinuation and at 14 and 28 days following treatment discontinuation.

[f] Collection of these analytes must occur **at the same time of day (± 1 hour)** at the Baseline (Visit 1) and at each subsequent visit (every 6 months) **for males only**. For example, if collected at the Baseline Visit at 9 AM, the Final Treatment/Early Termination Visit sample must be collected between 8 and 10 AM.

[g] 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 and within 28 days of discontinuing investigational product.

[h] The visit window of ± 1 day for the ATEP is based off the first visit (Visit 1) of the ATEP – any days out of visit window from a subject's involvement in Part 1 should be reset upon their enrollment into the ATEP.

[i] Subjects who discontinue early or complete the treatment period enter into the Observational Follow-up Phase.

[j] If a subject is planning to receive a primary booster dose of pneumococcal, tetanus, or influenza vaccine at any time during the study, a prevaccination blood sample should be obtained to measure the prevaccination titer.

6. PROCEDURES

Study Entry

Required assessments will be completed as depicted in Table 1 and Table 2.

- 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 sub-study portion of the ICD (the Intensive PK sub-study) prior to the initiation of any study procedures and indicate whether or not they consent to participate in this portion of the study. All subjects entering the ATEP will have to provide informed consent in order to participate.
- Relevant medical history (including relevant GI symptoms, neurological symptoms, alcohol and tobacco use, etc) information will be collected for each subject.
- Information regarding prior/concomitant medication usage will be collected for each subject. At the screening and baseline visits, concomitant medications should be checked against the list of prohibited medications to ensure required washout times have been met. If a subject does not meet the medication washout requirements, the study visit must be rescheduled.

Safety Assessments

Note: On the days of study visits, subjects will take their IP dose at the site.

Required assessments will be completed as depicted in Table 1 and Table 2. Assessments may be conducted at other times during the study if felt to be clinically warranted by the Investigator. The safety assessments may be conducted by a physician, physician assistant, nurse practitioner, or study nurse. Ideally, the safety assessor should be the same individual throughout the course of each subject's participation at a site.

- Information regarding all AEs regardless of causal relationship to IP (CC-220 or placebo), occurring at any time for the duration of the study, from the time of signing the ICD up to and including the Observation Phase, will be collected.
- Vital signs include temperature, pulse, and seated blood pressure. These will be collected at every visit. Blood pressure will be measured after the subject has been seated and resting quietly for 5 minutes.

  Note: On study visits where ECGs and PK evaluations are performed, blood pressure measurements should be completed first. Pre-dose ECGs should then be performed, followed by pre-dose PK blood draws and IP dosing.
- Complete physical examinations will include height (Screening Visit) and weight (frequency of collection will dependent on the phase of the study - to be done in street clothes, no shoes), skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal system evaluations. For the ATEP, weight and waist circumference (measured at both the umbilicus and the level of the anterior iliac crests) will be obtained **at every visit**. 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 e-CRF as medical history; clinically significant findings identified during the final treatment visit physical examination will be recorded as adverse events. Gynecological and urogenital examinations will not be done unless for cause.

- Targeted physical examinations will include evaluation of the skin, respiratory, cardiovascular, lymphatic, and musculoskeletal systems. Results of the physical examinations will be recorded only in the source documents. Clinically significant abnormal findings identified during the targeted physical examinations will be recorded on the eCRF as adverse events. Gynecological and urogenital examinations will not be done unless for cause. For the ATEP, weight and waist circumference (measured at both the umbilicus and the level of the anterior iliac crests) will be obtained **at every visit**.
- Standard 12-lead ECGs will be obtained at most study visits. In cases where ECG and PK timepoints coincide, a ±15 minute window will be allowed for assessment completion (ECG should always be assessed first). All ECGs from Visit 2 onward should be performed ≤ 15 minutes apart after the subject has been in the supine position for 3 minutes.
  - At Screening: one ECG will be performed
  - At required treatment visits: 3 ECGs will be done pre-dose
  - In the Observational Follow-up Phase: one ECG will be performed

  Stimulatory agents and/or medications, eg, caffeine, energy drinks, licorice, theophylline, etc, should be avoided prior to ECG administration.

  The same ECG equipment will be used throughout the study. 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 Bazett's and Fridericia's formula.
- Laboratory Assessments
  - Pregnancy testing (urine and/or serum) for all FCBP
  - Chemistry (including total protein, albumin, calcium, phosphorus, glucose, uric acid, total bilirubin, alkaline phosphatase, AST [SGOT], ALT [SGPT], lipase, amylase, sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, lactate dehydrogenase, [LDH], magnesium)
  - Hematology (complete blood count with differential and platelets, absolute white blood cell counts)
  - Apolipoproteins, total cholesterol and lipid-soluble vitamins (A, D, E, K)
  - Prothrombin time (PT); internationalized normalized ratio (INR); partial thromboplastin time (PTT)
  - Urinalysis (microscopic and quantitative protein)

- eGFR, protein creatinine ratio
- Tetanus toxoid, pneumococcal, and influenza titers
- Inflammation panel (including erythrocyte sedimentation rate [ESR], fibrinogen, high sensitivity C-reactive protein [hs-CRP], serum amyloid A)
- Hepatitis screen (includes testing for hepatitis B surface antigen and antibody, hepatitis B core antibodies (IgG/IgM) and antibodies to hepatitis C)
- Quantitative assessment of immunoglobulins [immunoglobulin A (IgA), immunoglobulin M (IgM) and immunoglobulin G (IgG)]
- Lupus anti-phospholipid profile (lupus anticoagulant, anti-cardiolipin antibodies and phosphatidylserine)
- Testosterone, FSH and LH **for males only.** Collection of these analytes must occur at both the Baseline and Final Treatment/Early Termination Visits **at the same time of day (± 1 hour)**. For example, if collected at the Baseline Visit at 9 AM, the Final Treatment/Early Termination Visit sample must be collected between 8 and 10 AM. During the ATEP, testosterone, FSH and LH testing will be conducted every 6 months.

Detailed instructions for sample collection, processing, storage, shipping and handling will be provided to the sites in a separate manual.

- Ophthalmological examinations will be conducted by a qualified ophthalmologist. Testing will include visual acuity and slit lamp exams with fluorescein staining following pupillary dilation, focusing on the anterior chamber, iris and anterior vitreous (unless use of fluorescein is contraindicated, eg, due to hypersensitivity).
- Celgene Pregnancy Prevention Counseling Program (CPPCP)

Efficacy Assessments

CCI [redacted]

In the event that a subject has taken systemic analgesics or NSAIDs within 12 hours of a study visit and/or systemic anti-pruritics within 48 hours of a visit, their visit should be rescheduled. Health assessment questionnaires must 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. CLASI, Swollen and Tender Joint Counts, Hybrid SELENA SLEDAI, SLICC/ACR SLE Damage Index, PGA and BILAG 2004 assessments must be conducted by a physician, physician assistant, or qualified nurse practitioner. The trained investigator/sub-investigator conducting efficacy assessments should remain the same throughout the study.

- **CLASI Activity Score Assessment**

  The CLASI Activity Score (Appendix A) 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.

- **CLASI Damage Score Assessment**

  The CLASI Damage Score (Appendix A) 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.

- **Physician Global Assessment (PGA)**

  The PGA (Appendix C) 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

  This is a physician administered instrument used to gauge a subject's overall state of health. A 10% increase (0.3 points) is considered a clinically relevant worsening of disease.

- **Swollen and Tender Joint Count**

  Using this tool, joint tenderness and swelling will be noted as "present" or "absent," with no quantitation of severity (Appendix B). 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.

- **Hybrid SELENA SLEDAI**

  The hybrid SELENA SLEDAI (Appendix E) measures disease activity through assessment of 24 lupus manifestations using a weighted score of 1 to 8 points. A decrease of 4 or greater points in the Hybrid SELENA SLEDAI is considered clinically meaningful. A manifestation is recorded if it is present over the previous 10 days regardless of severity or whether it has improved or worsened. What

differentiates the hybrid SELENA SLEDAI from the SELENA SLEDAI is the definition of proteinuria. The Hybrid SELENA SLEDAI defines proteinuria as > 0.5 gm/24 hours – 'new onset or recent increase of more than 0.5 gm/24 hours' has been removed from the definition.

- **Pericardial/Pleuritic Numerical Pain Scale**

  Each scale (Appendix G) is scored using numerical values of 1 through 10 with 1 representing 'no pain' and 10 representing 'worst possible pain'. Both pain scales will be self-administered by the subject and gauge the severity of their SLE pain related to pericardial and pleuritic discomfort. Any indication from subjects or study assessments, aside from pain, which indicate clinically significant pericardial or pleuritic manifestations of SLE must be thoroughly investigated. If clinically significant SLE related complications are found, the subject should be discontinued from the study into the Observational Follow-up Period and treated appropriately.

- **SLICC/ACR SLE Damage Index**

  The SLICC/ACR Damage Index (Stoll, 2005; Appendix O) 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.

- **British Isles Lupus Assessment Group 2004 (BILAG)**

  The BILAG 2004 (Isenberg, 2005; Appendix P) 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). Disease activity is categorized into five levels, Grades A-E.

CCI [redacted]

- CCI
  [redacted]

- **Fatigue Visual Analog Scale**

  The Fatigue VAS (Gilboe, 2001; Appendix H) will evaluate SLE related fatigue using a 0-100 mm VAS scale. A Fatigue VAS will allow the subject to indicate the degree of SLE related fatigue they experienced over the previous week.

- CCI
  [redacted]

- CCI
  [redacted]

Other Assessments

Pharmacokinetics

All subjects will participate in sparse PK as a participant in the main study (unless they elect to participate in the intensive PK sub-study). Completion of intensive pharmacokinetics requires the subject to have consented using the sub-study informed consent form. Both intensive and sparse PK samples will be collected to evaluate CC-220 PK. CCI [redacted] Dosing and sample collection information including CC-220 dose level, dosing date, dosing time (24 hour clock), and actual PK blood sampling time (24 hour clock) should be accurately documented on the appropriate eCRF pages.

Part 1

Sparse PK Sampling

All other subjects who do not participate in the intensive PK portion of the study will have sparse PK samples collected.

Pharmacokinetic blood samples (approximately 12 mL total) will be collected in subjects (unless the site does not have PK capabilities) who do not participate in intensive PK sampling at the following timepoints:

- Days 15, 29, 57 and 85: one pre-dose sample per visit.

Intensive PK Sampling

Participation in the intensive PK assessment will be an optional sub-study for which a separate consent will be signed at screening. Frequent collection of PK blood samples (approximately 57 mL total) will be performed in approximately 4 subjects per treatment group (a total of 32 subjects at the minimum) at the following timepoints:

- Visit 2 (Baseline – Day 1): pre-dose (Time = 0 hours), 1, 2, 3, 4, between 6 and 8 hours and 24 hours (± 5 hours) after administration of IP.
- Visit 4 (Day 15): one pre-dose sample per visit
- Visit 6 (Day 29): pre-dose (Time = 0 hours), 1, 2, 3, 4, between 6 and 8 hours and 24 hours (± 5 hours) after administration of IP.
- Visits 8 and 10 (Days 57 and 85): one pre-dose sample per visit

The IVRS will be used to ensure inclusion of a minimum of 4 intensive PK participants per dose group.

Pharmacokinetic samples should be collected within the following collection windows:

- -30 to -5 minutes for the pre-dose sample
- ± 10 minutes for the samples collected at timepoints of 1 to 4 hours
- ± 20 minutes for the samples collected at the timepoint of between 6 and 8 hours
- ± 5 hours for the sample collected at the timepoint of 24 hours (this sample must be collected prior to the second dose)

At each timepoint, approximately 3 mL of blood will be collected. The CC-220 concentration in plasma will be determined. Specific details regarding the collection, processing, storage, and shipment of PK samples will be provided in a separate document.

On all PK visits, subjects must bring their IP to the study center and IP must be administered to subjects at the study center after the collection of the pre-dose PK blood sample. Subjects will be asked to report the date and time of their last IP dose (prior to the current study visit day) to the study staff during their visit at the study center. The IP dosing time on the day of the PK sample collection should also be documented by the study staff.

In cases where ECG and PK timepoints coincide, a ± 15 minute window will be allowed for completion of PK (the ECG should always be assessed first).

No PK will be measured in the ATEP.

CCI [redacted]

7. STUDY POPULATION

7.1. Number of Subjects and Sites

Part 1

Approximately 40 subjects (not including screen failures) will be enrolled at multiple (approximately 40) North American sites.

Active Treatment Extension Phase

Approximately 75% of subjects from Part 1 are projected to enroll into the ATEP. Of the subjects who enroll into the ATEP, approximately 60% are projected to complete the 2 year treatment phase. In total approximately 18 subjects are expected to complete the ATEP.

7.2. Inclusion Criteria

Note: All applicable inclusion and exclusion criteria must be evaluated at both the Screening and Baseline Visits. Subjects entering the ATEP must be re-evaluated for inclusion and exclusion criteria, with the exception of SELENA SLEDAI score.

Subjects may be re-screened twice. Laboratory values for eligibility criteria must be confirmed within 42 days prior to randomization (Baseline Visit Day 1).

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

7.2.1. Part 1

Age/Gender

1. Male or female 18 years of age or older
2. Understand and voluntarily sign an ICD prior to the initiation of any study related assessments/procedures
3. Able to adhere to the study visit schedule and other protocol requirements.

Disease Specific

4. The subject has an established diagnosis of systemic lupus erythematosus (SLE) as defined by the 1997 Update of the 1982 ACR Revised Criteria for Classification of SLE at screening (Appendix D). The diagnosis is fulfilled provided that at least 4 criteria are met or have been met in the past.
5. Disease history of SLE ≥ 6 months at baseline
6. A minimum Hybrid SELENA SLEDAI score of ≥ 4 points at Baseline[†].

Pregnancy

7. Females of childbearing potential (FCBP)[1] must:

[1] A female of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

- Have two negative pregnancy tests as verified by the study doctor prior to starting study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy. This applies even if the subject practices true abstinence* from heterosexual contact.
- Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis) or agree to use, and be able to comply with, effective contraception without interruption, 28 days prior to starting IP, during the study therapy (including dose interruptions), and for 28 days after discontinuation of study therapy.

8. Male subjects must:
   - Practice true abstinence* or agree to use a condom 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 IP discontinuation, even if he has undergone a successful vasectomy.
9. Male subjects must agree not to donate semen or sperm during therapy and for at least 90 days following the discontinuation of IP.
10. All subjects must:
    - Understand that the IP could have potential teratogenic risk
    - 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.

Concomitant Medications

11. If the subject is using oral corticosteroids, the daily dose must be less than or equal to 10 mg of prednisone or equivalent during the study; the dose must be stable over the 4 weeks preceding randomization and throughout the study.
12. Subjects taking hydroxychloroquine, chloroquine and/or quinacrine must be on a stable dose for at least 4 weeks prior to their baseline visit and throughout the study.
13. All subjects taking hydroxychloroquine, chloroquine or quinacrine during the study must have documentation of a normal ophthalmologic examination performed within 1 year of the Baseline Visit.

* 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.)

† The SELENA SLEDAI score may be used to qualify a subject at the Baseline Visit without receipt of labs performed as part of the SELENA SLEDAI as long as the subject demonstrates a minimum score of 4.

14. For subjects not taking corticosteroids, or antimalarials, the last dose (in case of previous use) must be at least 4 weeks prior to screening.

7.2.2. Active Treatment Extension Phase

Age/Gender

1. Male or female 18 years of age or older

15. Understand and voluntarily sign an ICD prior to the initiation of any study related assessments/procedures

16. Able to adhere to the study visit schedule and other protocol requirements.

Pregnancy

17. Females of childbearing potential (FCBP)[2] must:

- Have two negative pregnancy tests as verified by the study doctor prior to starting study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy. This applies even if the subject practices true abstinence* from heterosexual contact.
- Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis) or agree to use, and be able to comply with, effective contraception without interruption, 28 days prior to starting IP, during the study therapy (including dose interruptions), and for 28 days after discontinuation of study therapy.

18. Male subjects must:

- Practice true abstinence* or agree to use a condom 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 IP discontinuation, even if he has undergone a successful vasectomy.

19. Male subjects must agree not to donate semen or sperm during therapy and for at least 90 days following the discontinuation of IP.

20. All subjects must:

- Understand that the IP could have potential teratogenic risk
- 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

[2] A female of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

* 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.)

- 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.

Concomitant Medications

21. If the subject is using oral corticosteroids, the daily dose must be less than or equal to 10 mg of prednisone or equivalent during the study; the dose must be stable over the 4 weeks preceding randomization and throughout the study.
22. Only use of topical steroids that fall into potency Classes 6 and 7 will be permitted during the study. No other topical, local or systemic treatments for dermatological manifestations of SLE will be permitted.
23. All subjects taking hydroxychloroquine, chloroquine or quinacrine during the study must have documentation of a normal ophthalmologic examination performed within 1 year of the Baseline Visit.
24. For subjects not taking corticosteroids the last dose (in case of previous use) must be at least 4 weeks prior to screening.

7.3. 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, subjects may have repeat assessments performed 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. Laboratory values for eligibility criteria must be confirmed within 42 days prior to randomization (baseline day 1). In the event a subject is entering the ATEP without undergoing the ATEP screening period, assessment of the criteria should be based off Visit 1 of the ATEP instead of screening

7.3.1. Part 1 and Active Treatment Extension Phase

Concomitant Medications and Procedures

1. The subject has been treated with intra-articular, intramuscular or IV pulse corticosteroids within 4 weeks of screening.
25. The subject has received high dose oral prednisone (> 100 mg/day) within 4 weeks of screening.
26. The subject has undergone plasmapheresis within 4 weeks of screening.
27. The subject has received methotrexate, sulfasalazine, leflunomide, tacrolimus, cyclosporine A, azathioprine, mycophenolate mofetil or iv immunoglobulin (IVIG) within 4 weeks of screening. **Note: methotrexate, sulfasalazine, ophthalmological cyclosporine or leflunomide will be permitted for concomitant use during the ATEP.**
28. Previous use of melphalan.
29. The subject has received cyclophosphamide within 8 weeks of screening.

30. Prior use of benlysta, abatacept, tocilizumab, adalimumab, infliximab, etanercept and other anti-TNF inhibitors within 12 weeks of screening.
31. The subject has been treated with biological therapy (eg, fusion proteins, therapeutic proteins, monoclonal antibodies or antibody fragments) within 8 weeks or 5 half-lives of screening.
32. The subject has received B-cell depleting or modulating agents, such as rituximab or anti-CD22 therapy, within 6 months prior to screening OR has received B-cell depleting agents from which the subject's B-cell count has not yet normalized (ie, CD20+ B-cell count is less than 200 and the absolute lymphocyte count [ALC] is less than 1500/µL).
33. St. John's Wort within one month of screening.
34. Strong inhibitors or inducers of CYP3A4/5 at least one week prior to dosing and during the course of study (Please refer to Appendix K for examples of medications). Grapefruit or related products ≤ 1 week prior to dosing and throughout the study.
35. The subject has participated in a clinical trial and has received an investigational product within 30 days, 5 pharmacokinetic half-lives or twice the duration of the biological effect of the investigational product (whichever is longer) prior to screening; OR participation in two or more investigational drug trials within 12 months of screening.
36. Unwilling to abstain from the use of prescription or non-prescription drugs, including: agents known to interact with CC-220, erythropoietin stimulation factors; herbal and dietary supplements (vitamins are permitted) or alternative medicine during study participation.
37. The subject has a planned or received immunization with a live or live attenuated vaccine within 2 months prior to administration of the first dose of IP and for 2 months after administration of the last dose of IP.
38. Have a planned surgical procedure or a history of any other medical disease laboratory abnormality, or condition that, in the opinion of the investigator, makes the subject unsuitable for the study.

Disease Severity

39. Unstable lupus nephritis defined as: eGFR of less than 50 mL/1.73 m^2.
40. CNS disease, including active severe CNS lupus (including seizures, psychosis, organic brain syndrome, cerebrovascular accident (CVA), cerebritis or CNS vasculitis) requiring therapeutic intervention within 6 months of screening.

Concomitant Disease

41. The subject has New York Heart Association (NYHA) Class III or IV congestive heart failure.
42. Presence of hepatitis B surface antigen (HBsAG). Subjects may have a positive anti-hepatitis B core antibody (anti-HBc) if the anti-hepatitis B surface antibody (anti-HBs) is positive as well (Appendix L). **Note**: for the ATEP, this exclusion will only apply to those subjects who come in for the ATEP greater than 14 days after their Part 1 Week 12 (Visit 10).

43. Antibodies to hepatitis C at Screening. **Note**: for the ATEP, this exclusion will only apply for those subjects who come in for the ATEP greater than 14 days after their Part 1 Week 12 (Visit 10).
44. The subject has a known positive history of antibodies to human immunodeficiency virus (HIV) or HIV disease or acquired immune deficiency syndrome (AIDs).
45. Has a history of an organ transplant (eg, heart, lung, kidney, liver) or hematopoietic stem cell/marrow transplant.
46. Malignancy or history of malignancy, except for:
    - treated (ie, cured) basal cell or squamous cell in situ skin carcinomas;
    - treated (ie, cured) cervical intraepithelial neoplasia (CIN) or carcinoma in situ of the cervix with no evidence of recurrence within 5 years of Screening
47. Systemic bacterial infections requiring treatment with oral or injectable antibiotics, or significant viral or fungal infections, within 4 weeks of Screening. Any treatment for such infections must have been completed and the infection cured, at least 2 weeks prior to Screening and no new or recurrent infections prior to the Baseline visit.
48. History of venous thrombosis or any thromboembolic events within 2 years of screening.
49. Clinical evidence of significant unstable or uncontrolled acute or chronic disease not due to SLE (ie, cardiovascular, pulmonary, hematologic, gastrointestinal, hepatic, renal, neurological, malignancy, psychiatric or infectious disease) which in the opinion of the investigator could put the subject at undue risk or confound study results.
50. Presence of active uveitis or any other clinically significant ophthalmological finding.
51. History or current diagnosis of peripheral neuropathy.

Laboratory Criteria

52. Hematology:
    - Neutrophil count $\leq 1.5 \times 10^9$/L (subjects entering the ATEP within 14 days can have a neutrophil count as low as 1.0×10^9/L)
    - Hb ≤ 9 g/dL
    - Lymphocyte count $\leq 500/mm^3$ or 0.50×10^9/L
    - Platelet count $\leq 100 \times 10^9$/L
    - Serum immunoglobulin (Ig) levels: IgG $\leq$ the lower limit of normal (LLN)
    - Liver function tests:
      – Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $\geq$ 2x upper limit of normal (ULN)
      – Alkaline phosphatase and bilirubin > 1.5 x ULN (isolated bilirubin > 1.5 ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%).
53. Any clinically significant abnormalities on ECG, which, in the opinion of the investigator would interfere with safe participation in the study.

General

54. The subject is unlikely to comply with the study protocol or is unsuitable for any other reason, as judged by the investigator or medical monitor.
55. Substance dependence or abuse within six months of the Screening Visit which, in the opinion of the investigator, would interfere with the patient's safety or ability to comply with the study procedures.
56. History of sensitivity to any of the investigational products/placebo, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation. The subject has a history of severe allergic reactions to or hypersensitivity to any component of the IP or placebo.
57. History of tuberculosis (TB). Subjects with a history of TB who have completed a standard course of treatment (documented) are eligible for study entry.
58. Pregnant or nursing (breast-feeding) females.

8. DESCRIPTION OF STUDY TREATMENTS

8.1. 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. CC-220 will be provided by the sponsor in a 0.3 mg formulated capsule CCI. In addition, the sponsor will provide matching placebo identical in appearance to CC-220 0.3 mg formulated capsule. Excipients of the formulation include CCI

8.2. Treatment Administration and Schedule

8.2.1. Dose Modification or Interruption

Subjects will remain on their assigned treatment for up to 12 weeks in Part 1 and up to 100 weeks for the ATEP.

In the event a subject experiences clinically significant IP-related adverse events, a dose interruption for up to 14 days will be permitted (see Section 12.1). If a subject is able to recover from their IP-related adverse event per Section 12.1, he/she will reduce their dose to the next lowest dosing regimen. Dose reductions will occur as follows:

- Subjects on 0.6 mg QD will reduce their dose to 0.6 mg/0.3 mg on alternating days
- Subjects on 0.6 mg/0.3 mg on alternating days will reduce their dose to 0.3 mg QD
- Subjects on 0.3 mg QD will:
  - reduce their dose to 0.3 mg QOD (Part 1 only)
  - be terminated from the study (ATEP only)
- Subjects on 0.3 mg QOD will reduce their dose to placebo (Part 1 only)

A subject will only be permitted to reduce their dose one time during the study. Subjects who originally came into the ATEP on 0.6 mg QD and dose reduce to 0.6/0.3 mg QD on alternating days upon implementation of Protocol Amendment 5 will be eligible for one additional dose reduction during the ATEP. The decision to modify IP dosing will be based on the rules provided in Section 12.1. The sponsor should be notified of the intent to dose reduce prior to a change in dosing.

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.

8.2.2. Overdose

Overdose, as defined for this protocol, applies to protocol-required dosing of the IP 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 overdose definition will apply to only CC-220 (or matching placebo). Other required or optional non-IP intended for prophylaxis of certain side effects, etc, are excluded from this definition. Overdose for this protocol, on a per dose basis, is defined as ingestion of ≥ 4 capsules of CC-220 (or matching placebo) in any 24-hour period whether by accident or intentionally. Adverse Events associated with an overdose must be collected on the Adverse Events page of the CRF for all overdosed subjects, but the overdose itself is not considered an AE.

8.3. Method of Treatment Assignment

After the informed consents have been signed, subjects will be assigned a subject ID by IVRS 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. At the Baseline Visit (Day 1), subjects who meet the eligibility criteria shall be enrolled using IVRS to receive either the assigned CC-220 dose or placebo.

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 0022002). 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 0023002).

Designated study personnel at the investigational sites will be assigned password protected, coded identification numbers, which give them authorization to call into the IVRS to enroll and/or randomize subjects, as well as re-supply and discontinue subjects from the study. 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, the IVRS will assign a subject ID number. Confirmation of the subject ID will be sent to the investigational site, Celgene and/or its representative.

During the study, the pharmacy or authorized study personnel at the investigational site will dispense coded investigational product kits in accordance with the randomization number assigned by the IVRS. Authorized personnel will call IVRS to confirm the medication number assigned to the subject at the time of or prior to dispensing to a subject.

8.4. Packaging and Labeling

The Investigator(s) or designee(s) is responsible for accounting for all IP that is issued to and returned by the subject during the course of the study.

The Investigator(s) or designee (s) is responsible for taking an inventory of each IP shipment received and comparing it with the accompanying IP accountability form. The Investigator(s) or designee (s) will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file and return a copy to Celgene. 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.

Celgene will instruct the Investigator on the return, disposal and/or destruction of investigational product and/or medical device materials if applicable.

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

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.

8.5. Investigational Product Accountability and Disposal

Celgene (or designee) will review with the Investigator and relevant site personnel the process for Investigational Product return, disposal, and/or destruction including responsibilities for the site vs. Celgene (or designee).

8.6. 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.

Overall compliance is defined as taking between 75% and 120% of dispensed IP. In the event of gross compliance problems (eg, missing more than 4 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) sponsor must be contacted to decide whether dosing should resume or whether the subject should be terminated from the study and enter into the Observational Follow-up Period.

9. CONCOMITANT MEDICATIONS AND PROCEDURES

9.1. Permitted Concomitant Medications and Procedures

Use of the following concomitant medications is permitted. These include:

- ≤ 10 mg/day of oral prednisone (or equivalent) and the dose must remain stable for the duration of the subject's study participation
- Inhaled corticosteroids for use in a disease other than lupus, eg, asthma, will be allowed.
- Only use of topical steroids that fall into potency classes 6 and 7 will be permitted during the study.
- Oral NSAIDs may be used, but must be stopped 12 hours prior to all study visits.
- Concurrent treatment with stable doses of hydroxychloroquine, chloroquine, or quinacrine will be permitted, provided the subject has been on a stable dose for at least 4 weeks prior to their baseline visit and remains on the same dose throughout the study. Subjects participating in the ATEP will be permitted to modify or stop their antimalarial treatment at any time.
- Systemic analgesics or systemic anti-pruritic medications (**systemic analgesics must be stopped 12 hours prior to all study visits and systemic anti-pruritics 48 hours prior to all study visits**)
- One-a-day vitamins recommended by the physician for a deficiency are permitted.
- Thromboprophylaxis with low dose aspirin, low molecular weight heparin or other equivalent antithrombotic or anticoagulant is required unless the investigator determines that, based on the totality of the subjects' risk factors for thrombosis, thromboprophylaxis is not required or is contraindicated.

  If any additional prophylaxis is needed, it should be based on the local standard of care and the investigator's best judgement after careful consideration of the benefit versus the potential risk for the individual subject.
- Granulocyte-macrophage colony stimulating factor (GM-CSF) may be prescribed by the investigator, if appropriate, to treat a subject who discontinues from IP as a result of an ANC of < 1000 cells/μL (1.0×10^9/L). This subject must enter the Post-treatment Observational Follow-up Phase of the study.
- Methotrexate (7.5 mg – 25 mg per week), leflunomide (maintenance dosing must not exceed 20 mg daily), sulfasalazine (dosing not to exceed 3 g daily) or ophthalmologic cyclosporine will be permitted during the ATEP.

Subjects must check with study personnel before initiating the use of prescribed or over-the-counter medications during the study.

Medication doses and treatment regimens should remain generally stable throughout the course of the study.

In the event a subject requires a surgical or invasive procedure during the course of the study, the sponsor must be contacted to discuss whether or not the subject is eligible to continue.

9.2. Prohibited Concomitant Medications and Procedures

Refer to Section 7.3 for a comprehensive list of prohibited concomitant medications and procedures.

9.3. Required Concomitant Medications and Procedures

Thromboprophylaxis with low dose aspirin, low molecular weight heparin or other equivalent antithrombotic or anticoagulant is required unless the investigator determines that, based on the totality of the subjects' risk factors for thrombosis, thromboprophylaxis is not required or is contraindicated.

10. STATISTICAL ANALYSES

10.1. Overview

The primary objective of the statistical analysis for Part 1 is to evaluate the safety and tolerability of CC-220 for subjects with SLE.

For Part 1, the placebo treated subjects in the three dose groups will be merged and will be considered as a one treatment group in the final efficacy and safety analyses.

For the ATEP, the treatment groups will be combined from Part 1 and the ATEP to form one treatment group for each dose level/regimen. Additionally, all treatment groups will be combined into a total group.

10.2. Study Population Definitions

Safety analyses will be based on the safety population, which will include all subjects who are randomized and receive at least one dose of IP. Subjects will be included in the treatment group corresponding to the IP they actually received for the analyses using the safety population. For most subjects, this will be the treatment group to which they are randomized. Subjects who take an IP that differs from the assigned one, according to the randomization schedule, the entire Double-blind Placebo-controlled period will be included in the treatment group corresponding to the IP they actually received.

CCI [redacted] The ITT analysis set will consist of all subjects who are randomized as specified in the protocol and receive at least one dose of IP. Subjects who are randomized in error and who do not receive any dose of IP will be excluded from the ITT analysis set. Subjects will be included in the treatment group to which they are randomized for the ITT analyses.

The per protocol (PP) analysis set will consist of all subjects included in the ITT analysis set who have at least one post-baseline efficacy evaluation and no critical protocol violations as described in the SAP.

The PK population will include all subjects in the safety population with at least one non-missing plasma concentration data. All analysis of PK data will be based on the PK population and subjects will be analyzed according to the treatment group to which they were randomized.

CCI [redacted]

10.3. Sample Size and Power Considerations

For Part 1, a total of approximately 40 subjects in total will be randomized into 4 dose groups with a 4:1 ratio of CC-220 (0.3 mg QOD, 0.3 mg QD, 0.6/0.3 mg alternating QD, 0.6 mg QD) or matching placebo (8 subjects in the CC-220 arm and 2 subjects in the placebo arm for each dose group) using an IVRS.

The sample size was based on prior clinical experience and no formal sample size or power calculation was performed.

10.4. 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.

10.5. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for both treatment and follow-up phases. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

10.6. Efficacy Analysis

No multiplicity adjustment will be conducted for this Phase 2 pilot study. Therefore, p-values and CIs from any efficacy analyses should be interpreted with caution. They should be used as measures of strength of association between treatment effect and endpoint, rather than formal criteria to claim statistical significance. All efficacy analyses will be conducted using the ITT population.

CCI [redacted]

Active Treatment Extension Phase

Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) for baseline, specified time points, and change from baseline in efficacy measures with continuous variables will be summarized by visit and by initial treatment group in Part 1. No p-values will be provided other than the descriptive statistics. Missing data will not be imputed and only observed results will be utilized. CCI [redacted]

Proportion and frequency of the subjects for the hierarchical data will be summarized by visit (if applicable) by initial treatment group in Part 1, and combined similar to continuous variables. No p-values will be provided. Missing data will not be imputed and only observed results will be utilized.

10.7. Safety Analysis

The safety analyses will be performed using the safety population as defined in Section 10.2.

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA) coding system. Adverse events occurring during the Treatment Phase and the Observation Phase will be tabulated for each Part 1. 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, including weight, 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.

10.8. Interim Analysis

Part 1

Following completion of the first 28 days of the Treatment Phase by 8 subjects of each dose group, assessments of safety and tolerability will be conducted. Unblinded interim analyses may be performed by a group that is independent of the study team for administrative purposes, which includes the potential to discontinue any treatment group. If conducted, the details of this analysis including the scope of distribution will be documented in a separate charter/analysis plan.

10.9. Other Topics

10.9.1. Pharmacokinetic Analysis

The Pharmacokinetic analysis will be performed using the PK population as defined in Section 10.2.

Pharmacokinetic parameters (AUC, C_{max}, t_{max}, $t_{1/2}$. CL/F and V_z/F) in plasma will be estimated from the CC-220 versus time data using noncompartmental analysis. Descriptive statistics will be provided for CC-220 concentrations and PK parameters, and the results will be presented in tabular and graphic form as appropriate. CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

11. ADVERSE EVENTS

11.1. Monitoring, Recording and Reporting of Adverse Events

An adverse event (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 11.3), regardless of etiology. Any worsening (ie, 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.

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 8.2.2 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 an 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 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 84 days after the last dose of IP for Part 1 and until 28 days after the last dose of IP for the ATEP, and those SAEs made known to the investigator at any time thereafter that are suspected of being related to IP. AEs and serious adverse events (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.

11.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

11.2.1. Seriousness

A serious adverse event (SAE) is any AE occurring at any dose that:

- Results in death;

- Is life-threatening (ie, 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.
- An elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, that has not worsened from baseline.
- A procedure that is planned (ie, planned prior to starting 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.
- 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 IP, action taken regarding IP, and outcome.

11.2.2. Severity / Intensity

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

The severity of AEs will be graded based upon the subject's symptoms according to the following scale:

Mild

- Asymptomatic or mild symptoms; clinical or diagnostic observations only
- Intervention not indicated
- Activities of daily living (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 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.

11.2.3. Causality

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

Not suspected: Means 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: Means 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 Celgene, please provide the name of the manufacturer when reporting the event.

11.2.4. Duration

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

11.2.5. Action Taken

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

11.2.6. Outcome

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae or death (due to the SAE). The investigator will report the outcome of the event for both AEs and SAEs.

11.3. 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).

11.4. Pregnancy

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.

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

11.4.1. Females of Childbearing Potential:

Pregnancies and suspected pregnancies (including elevated β-HCG or a positive pregnancy test in a female of childbearing potential regardless of disease state) occurring while the subject is on IP, or within 28 days of the subject's last dose of IP, 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 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.

11.4.2. Male Subjects

If a female partner of a male subject taking investigational product 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.

11.5. 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, 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 the last study visit [84 days after the last dose of IP for Part 1 and 28 days after the last dose of IP for the ATEP]) or any SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP. SAEs 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 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 Celgene and the IRB/EC.

11.5.1. 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.

11.6. 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 serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

Celgene 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 (ie, 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 Celgene and the IRB/EC. (See Section 15.3 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.

12. DISCONTINUATIONS

12.1. Subject Stopping Rules

Laboratory

– Presence of any of the following laboratory results will require repeat testing within 3 to 7 days of the original test. Subjects should withhold their prescribed IP dose pending receipt of their repeat test results. If the result(s) demonstrate that the subject's laboratories have normalized, they may continue in the study at a reduced dose (see Section 8.2.1). If the result(s) fall within the specified stopping rule criteria listed below, an additional retest within 11 to 14 days of the original result will be permitted (IP should continue to be withheld during this re-testing period). If, after 11 to 14 days, the result(s) falls within the criteria below, subjects are required to be discontinued from the study. If the result(s) demonstrate that the subject's laboratories have normalized, they may continue in the study at a reduced dose (see Section 8.2.1).

Laboratories for subjects exhibiting the following criteria must be repeated within 3 days:

- White blood cells (WBC) ≤ 1500/mm^3 (≤ 1.5 x 10^9/L) or ≥ 16,000/mm^3 (≥ 16 x 10^9/L)
- Platelet count ≤ 75,000/µL (≤ 75 x 10^9/L)
- Absolute neutrophil count (ANC) ≤ 1000 cells/µL (1.0 x 10^9/L)

Granulocyte-macrophage colony stimulating factor (GM-CSF) may be prescribed by the investigator, if appropriate, to treat a subject who discontinues from IP as a result of an ANC of < 1000 cells/µL (1.0 x 10^9/L). This subject must enter the Post-treatment Observational Follow-up Phase of the study.

- MDRD eGFR < 30 mL/min
- AST/SGOT or ALT/SGPT ≥ 5 x ULN
- AST/SGOT or ALT/SGPT > 3 x ULN **and** total bilirubin > 2 x ULN

Laboratories for subject exhibiting the following criteria must be repeated within 7 days:

- AST/SGOT or ALT/SGPT > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or:
  - Eosinophilia (> 7%) **Note**: for subjects in the ATEP eosinophilia must be greater than 12%.
  - Hemoglobin ≤ 8 g/dL
  - Total bilirubin ≥ 2.5 mg/dL

Development of the Following Adverse Events/SAEs

- Recurrent infections requiring in-patient treatment and/or parenteral antibiotics
- A thromboembolic event (eg, deep vein thrombosis, thrombotic cerebrovascular or cardiovascular events)
- Peripheral neuropathy
- Life-threatening or disabling rash or blistering
- Uveitis or other clinically significant ophthalmological findings
- Pregnancy

The continued eligibility of subjects who experience the following events should be discussed with the Medical Monitor to determine if the subject is eligible to continue in the study. The Medical Monitor should be contacted or the Sponsor should be consulted concerning any subject that has an AE leading to drug interruption lasting for more than 4 days.

– Other SAEs (eg, potential drug reaction or allergy)

– Presence of any other new onset, severe organ/system manifestations that interfere with activities of daily living, require medical intervention(s) for ≥ 7 days and/or hospitalization

– Any prolonged infection with symptoms lasting greater than two weeks and/or requiring antibiotic treatment greater than 10 days in duration

Note: Only one dose reduction will be permitted per subject (with the exception of those subjects entering the ATEP on 0.6 mg QD who must be dose reduced based upon Protocol Amendment 5 and who will be eligible for one additional dose reduction in the ATEP). Any laboratory values which fall into the subject stopping criteria following a dose reduction require discontinuation of the subject from the study.

12.2. Dose Group Stopping Rules

The cumulative safety data for a dose group will be reviewed on a regular basis, including the number of subjects who met the above stopping rules after each dose group completes dosing. If 3 or more subjects experience a severe or serious AE which leads to discontinuation, the safety management team (SMT) will be notified and the sponsor will determine if dose escalation will be stopped.

12.3. Discontinuation Criteria

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

- Adverse event(s)
- Lack of therapeutic effect

- Withdrawal of consent
- Death
- Lost to follow-up
- Protocol violation

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

Celgene is to be notified of all discontinuations from IP.

Subjects who discontinue from the study prior to completing 28 days of treatment may be replaced at the discretion of the sponsor.

13. EMERGENCY PROCEDURES

13.1. 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 Celgene/CRO 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.

13.2. 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 thorough the IVRS by using an emergency unblinding personal identification number (PIN), and the investigator should call IVRS for unblinded dose information.

14. REGULATORY CONSIDERATIONS

14.1. 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 Celgene, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (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.

14.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene 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. 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 document 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.

At the time results of this study are made available to the public, Celgene 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.

14.3. 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 informed consent document 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 informed consent document 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 informed

consent document. The revised informed consent document 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.

14.4. Confidentiality

Celgene 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). Celgene requires the Investigator to permit Celgene'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 informed consent document, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

14.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene 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.

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

Before the start of the study, the study protocol, informed consent document, 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 Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by Celgene 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 informed consent document 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 Celgene and the IRB/EC prior to use.

14.7. 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.

14.8. Closure of the Study

Celgene reserves the right to terminate this study 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 Celgene 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.

15. DATA HANDLING AND RECORDKEEPING

15.1. 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.

15.2. Data Management

Data will be collected via eCRF and entered into the clinical database per Celgene 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.

15.3. Record Retention

Essential documents must be retained by the Investigator for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. 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 informed consent documents 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, Celgene, 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 Celgene 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 Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene 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/Institution should take measures to prevent accidental or premature destruction of these documents.

16. QUALITY CONTROL AND QUALITY ASSURANCE

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

16.1. Study Monitoring and Source Data Verification

Celgene 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 investigator meeting. Prior to enrolling subjects into the study, a Celgene 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 Celgene 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.

16.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene 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/IECs, 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 Celgene immediately.

17. PUBLICATIONS

The results of this study may be published in a medical publication, journal, or may be used for 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. CCI [redacted]

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19. APPENDICES

APPENDIX A. THE CUTANEOUS LUPUS AREA AND SEVERITY INDEX

Cutaneous LE Disease Area and Severity Index (CLASI)

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

activity ⟵ ⟶ **damage**

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

Mucous membrane

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

Dyspigmentation

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

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

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

Alopecia

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

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

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

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

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

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

APPENDIX B. SWOLLEN AND TENDER JOINT COUNT – 44 JOINTS

44 Joint Score: Upper Extremity Joint Counts

Please write in the appropriate code for every joint using the Pain/Tenderness and Swelling Codes.

Pain/Tenderness Codes

Y = Pain/tenderness
N = No pain/tenderness
ND = Not Done

Swelling Codes

Y = Swelling
N = No swelling
ND = Not Done

Joints	Right Side		Left Side	
	Pain/Tenderness	Swelling	Pain/Tenderness	Swelling
	Y N ND	Y N ND	Y N ND	Y N ND
Sternoclavicular				
Acromioclavicular				
Shoulder				
Elbow				
Wrist				
MCPC 1				
MCP 2				
MCP 3				
MCP 4				
MCP 5				
PIP 1				
PIP 2				
PIP 3				
PIP 4				
PIP 5				

APPENDIX B. SWOLLEN AND TENDER JOINT COUNT – 44 JOINTS (Continued)

44 Joint Score: Lower Extremity Joint Counts

Please write in the appropriate code for every joint using the Pain/Tenderness and Swelling Codes.

Pain/Tenderness Codes

Y = Pain/tenderness
N = No pain/tenderness
ND = Not Done

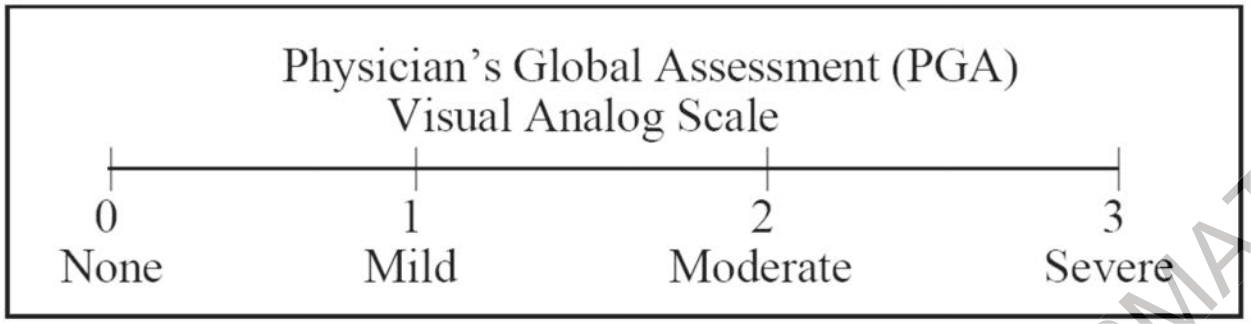
Swelling Codes

Y = Swelling
N = No swelling
ND= Not Done

Joints	Right Side				Left Side			
	Pain/Tenderness		Swelling		Pain/Tenderness		Swelling	
	Y N ND		Y N ND		Y N ND		Y N ND	
Knee								
Ankle								
MTP 1								
MTP 2								
MTP 3								
MTP 4								
MTP 5								

Sieper, 2009.

APPENDIX C. PHYSICIAN'S GLOBAL ASSESSMENT



APPENDIX D. 1997 UPDATE OF THE 1982 ACR REVISED CRITERIA FOR CLASSIFICATION OF SLE

1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus

Criterion	Definition
1. Malar Rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive Arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or Pericarditis	1. Pleuritis--convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion 1. *OR* 2. Pericarditis--documented by electrocardigram or rub or evidence of pericardial effusion
7. Renal Disorder	1. Persistent proteinuria > 0.5 grams per day or > than 3+ if quantitation not performed 1. *OR* 2. Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic Disorder	1. Seizures--in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance 1. *OR* 2. Psychosis--in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic Disorder	1. Hemolytic anemia--with reticulocytosis 1. *OR*

APPENDIX D. 1997 UPDATE OF THE 1982 ACR REVISED CRITERIA FOR CLASSIFICATION OF SLE (Continued)

Criterion	Definition
	2. Leukopenia--< 4,000/mm^3 on ≥ 2 occasions 1. *OR* 3. Lyphopenia--< 1,500/ mm^3 on ≥ 2 occasions 1. *OR* 4. Thrombocytopenia--<100,000/ mm^3 in the absence of offending drugs
10. Immunologic Disorder	1. Anti-DNA: antibody to native DNA in abnormal titer 1. *OR* 2. Anti-Sm: presence of antibody to Sm nuclear antigen 1. *OR* 3. Positive finding of antiphospholipid antibodies on: 1. 1. an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2. 2. a positive test result for lupus anticoagulant using a standard method, or 3. 3. a false-positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Positive Antinuclear Antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

APPENDIX E. HYBRID SELENA SLEDAI

Hybrid SLEDAI (4 wk or 10 day assessment allowed)

Name/ID number: **Date of Assessment:**

(Circle in SLEDAI Score column if descriptor is present at the time of the visit or in the preceding 4 weeks) (The same instrument can also be used going back only ten days)

Item no.	SLEDAI SCORE	Descriptor	Definition
1	8	**Seizure**	Recent onset, exclude metabolic, infectious or drug causes
2	8	**Psychosis**	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganised, or catatonic behaviour. Exclude uraemia and drug causes
3	8	**Organic brain syndrome**	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes
4	8	**Visual disturbance**	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudates or hemorrhages in the choroid, or optic neuritis, scleritis or episcleritis. Exclude hypertension, infection, or drug causes
5	8	**Cranial nerve disorder**	New onset of sensory or motor neuropathy involving cranial nerves
6	8	**Lupus headache**	Severe, persistent headache: may be migrainous, but must be non-responsive to narcotic analgesia THIS WOULD RARELY BE ATTRIBUTED TO SLE...ALMOST NEVER SCORED
7	8	**CVA**	New onset Cerebrovascular accident(s). Exclude arteriosclerosis
8	8	**Vasculitis**	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages or biopsy or angiogram proof of vasculitis
9	4	**Arthritis**	> 2 joints with pain and signs of inflammation (i.e. tenderness with swelling or effusion)
10	4	**Myositis**	Proximal muscle aching/weakness, associated with elevated creatinine phosphokinase (CK)/aldolase, or EMG changes or a biopsy showing myositis
11	4	**Urinary casts**	Heme-granular or RBC casts
12	4	**Hematuria**	> 5 RBC/high power field. Exclude stone, infection or other cause
13	4	**Proteinuria**	> 0.5 gram/24 hours
14	4	**Pyuria**	> 5 WBC/high power field. Exclude infection
15	2	**Rash**	Inflammatory type rash
16	2	**Alopecia**	Abnormal, patchy or diffuse loss of hair
17	2	**Mucosal ulcers**	Oral or nasal ulcerations
18	2	**Pleurisy**	Pleuritic chest pain or pleural rub or effusion, or pleural thickening (does not require an objective component if medically convincing)
19	2	**Pericarditis**	Classic pericardial pain and/or rub, effusion or ECG or echocardiogram confirmation (does not require an objective component if medically convincing)
20	2	**Low complement**	Decrease in CH50, C3 or C4 below lower limit of normal for testing laboratory
21	2	**Increased DNA binding**	Increased DNA binding above normal range for testing laboratory
22	1	**Fever**	> 38°C. Exclude infectious cause
23	1	**Thrombocytopenia**	< 100 x 10^9 platelets/L, exclude drug causes
24	1	**Leukopenia**	< 3 x 10^9 WBC/L, exclude drug causes

SCORE:

APPENDIX E. HYBRID SELENA SLEDAI (Continued)

Hybrid SLEDAI (4 wk or 10 day assessment allowed)

Name/ID number: **Date of Assessment:**

SELENA SLEDAI FLARE INDEX (Can be used with any version of the SLEDAI)

Physician's Global Assessment (PGA)
Visual Analog Scale with anchors

0	1	2	3
None	Mild	Moderate	Severe

(this is a three inch or 10 cm scale)

Mild or Moderate Flare ☐

- ☐ Change in SELENA-SLEDAI instrument score of 3 points or more (but not to more than 12)
- ☐ New/worse: Discoid, photosensitive, profundus, bullous lupus,
  Nasopharyngeal ulcers
  Pleuritis
  Pericarditis
  Arthritis
  Fever (SLE)
- ☐ Increase in prednisone, but not to >0.5 mg/kg/day
- ☐ Added NSAID or hydroxychloroquine for SLE activity
- ☐ ≥1.0 increase in PGA score, but not to more than 2.5

Severe Flare ☐

- ☐ Change in SELENA-SLEDAI instrument score to greater than 12
- ☐ New/worse: CNS-SLE
  cutaneous vasculitis,
  Vasculitis
  Nephritis
  Myositis
  Plt <60,000
  Hemolytic anemia: Hb <70 g/L or decrease in Hb >30 g/L

  Requiring: double prednisone, or prednisone increase to >0.5 mg/kg/day, or hospitalization
- ☐ Increase in prednisone to >0.5 mg/kg/day
- ☐ New cyclophosphamide, azathioprine, methotrexate for SLE activity
- ☐ Hospitalization for SLE activity
- ☐ Increase in Physician's Global Assessment score to >2.5

APPENDIX F. GILLIAM CLASSIFICATION

I. LE-non-specific rheumatological skin diseases
  A. Cutaneous vascular disease
    1 Vasculitis
      1.1 Leukocytoclastic
        1.1.1 Palpable purpura
        1.1.2 Urticarial vasculitis
        1.1.3 Periarteritis nodosa like cutaneous lesions
    2 Vasculopathy
      2.1 Degos' disease-like lesions
      2.2 Secondary atrophie blanche (livedoid vasculitis, livedo vasculitis)
      2.3 Periungual telangiectasia
      2.4 Livedo reticularis
      2.5 Thrombophlebitis
      2.6 Raynaud's phenomenon
      2.7 Erythromelalgia (erythermalgia)
  B. Nonscarring alopecia
    1 Lupus hair
    2 Telogen effluvium
    3 Alopecia areata
  C. Sclerodactyly
  D. Rheumatoid nodules
  E. Calcinosis cutis
  F. LE-nonspecific bullous lesions
  G. Urticaria
  H. Papulonodular mucinosis
  I. Cutis laxa/anetoderma
  J. Acanthosis nigricans
II. LE-Specific Skin Diseases
  A. Acute cutaneous LE [ACLE]
    1 Localised ACLE
    2 Generalised ACLE
  B. Subacute cutaneous LE [SCLE]
    1 Annular SCLE
    2 Papulosquamous SCLE
  C. Chronic cutaneous LE (CCLE)
    1 Classic discoid LE [DLE]
      1.1 Localised DLE
      1.2 Generalised DLE
    2 Hypertrophic/verrucous DLE
    3 Lupus profundus/lupus panniculitis
    4 Mucosal
      4.1 Oral
      4.2 Conjunctival
    5 Lupus tumidus (urticarial plaque of LE)
    6 Chilblain LE (chilblain lupus)
    7 Lichenoid DLE (LE/lichen planus overlap)

APPENDIX F. GILLIAM CLASSIFICATION (Continued)

Introduction

The Gilliam Classification of skin changes that are associated with lupus erythematosus (LE) will be employed to select patients for this study. This classification subdivides such skin changes into two broad categories – LE-specific and LE-nonspecific. LE-specific and LE-nonspecific skin lesions are distinct clinico-pathologic entities.

LE-specific skin lesions are characterized by a characteristic histopathologic pattern on biopsy known as the lichenoid tissue reaction/interface dermatitis. This histopathologic pattern has recently been shown to result from an interplay of aberrant innate and adaptive immune responses involving TLR-mediated plasmacytoid dendritic cell activation. The generation of interferon-a by these cells results in a gene activation profile that orchestrates the recruitment and activation of cytotoxic T cells that target and injure the epidermal basal cell layer.

There are three types of LE-specific: acute cutaneous LE, subacute cutaneous LE, and chronic cutaneous LE. Only patients displaying subacute cutaneous LE (SCLE) lesions and the classical discoid LE (DLE) variety of chronic cutaneous LE will be included in this study.

Clinical Description of LE-specific Skin Lesions To Be Studied

Classical DLE

The most common form of chronic cutaneous LE is classical DLE. Classical DLE skin lesions typically present as well-demarcated red-purple macules or papules that soon assume a superficial scale. As the lesions progress, they increases in size to coin-shaped (ie, discoid) plaques associated with a characteristic pattern of dyspigmentation. Especially prominent in darkly pigmented individuals, hyperpigmentation in observed at the active periphery of classical DLE lesions while hypopigmentation is seen in the inactive central parts of the lesions. As lesions evolve, adherent scales with extension into dilated hair follicles develop. The center of the lesion becomes depressed as a result of atrophic scarring with permanent loss of appendages including hair follicles. Scarring alopecia is a characteristic result of classical DLE lesions. Telangiectasia are typically observed at the atrophic scarring stage of DLE. Much less commonly, the DLE histopathological process presents clinically in variant morphological clinical forms. One example is the urticarial plaque type DLE lesion. Patients displaying such variant morphologies will not be included in this study.

Classical DLE lesions are most commonly found localized to the face, ears, and scalp in an asymmetrical distribution (ie, localized DLE). Less commonly, areas below the neck are affected including extensor aspect of the upper extremities, V-area of upper chest, and trunk (ie, generalized DLE).

Histopathology

Classical DLE

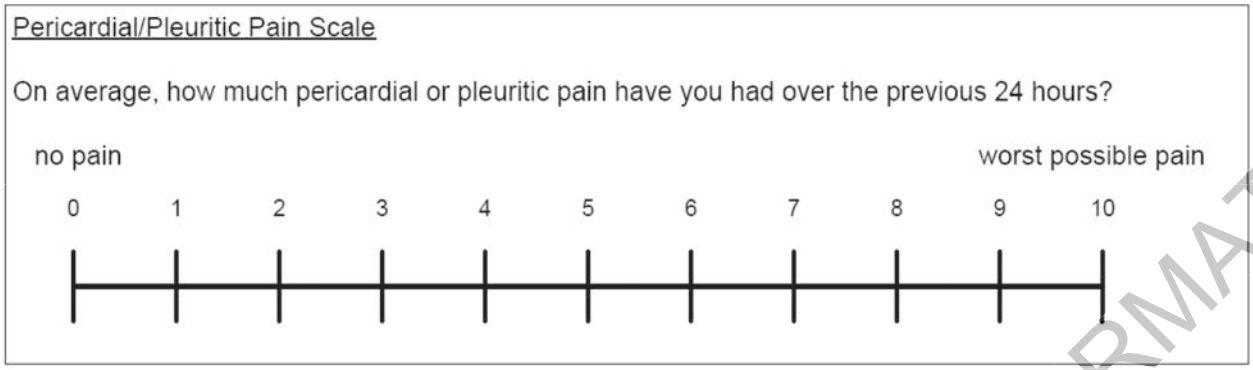
Classic DLE lesions demonstrates hyperkeratosis and follicular plugging. There is characteristic loss of organized basal epidermis, whereas the spinous layer of the epidermis may be atrophic. Other changes in the basal layer of the epidermis include edema, liquefactive degeneration,

APPENDIX F. GILLIAM CLASSIFICATION (Continued)

epidermal basement membrane thickening, increased formation of melanin pigment, and dermal pigment incontinence. There is a mononuclear cell infiltrate of macrophage and T lymphocytes in the dermis, with plasma cells in chronic lesions at times leading to significant mucin deposition. The inflammatory infiltrate can extend deeper compared with ACLE and SCLE lesions, with invasion into the reticular dermis. As mentioned earlier, there is evidence of high level interferon-a signaling within classical DLE and SCLE skin lesions.

(David-Bajar, 1997; Rothfield, 2006; Sontheimier, 1997).

APPENDIX G. PERICARDIAL/PLEURITIC NUMERICAL PAIN SCALE



APPENDIX H. FATIGUE VAS

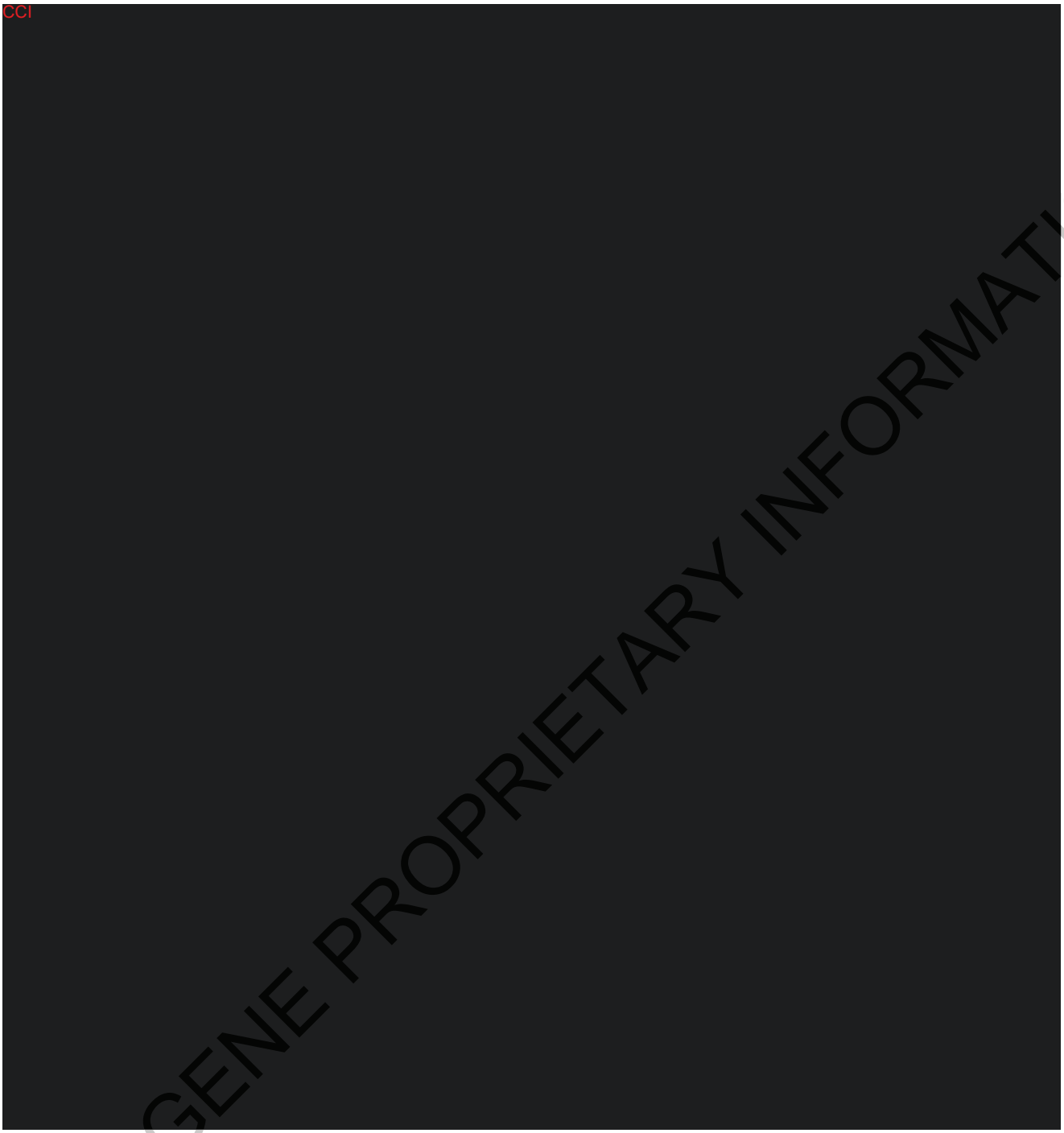
Visual Analog Scale of Fatigue

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

Please use vertical stroke

No Fatigue	Fatigue as bad as it could be
0	100

CCI



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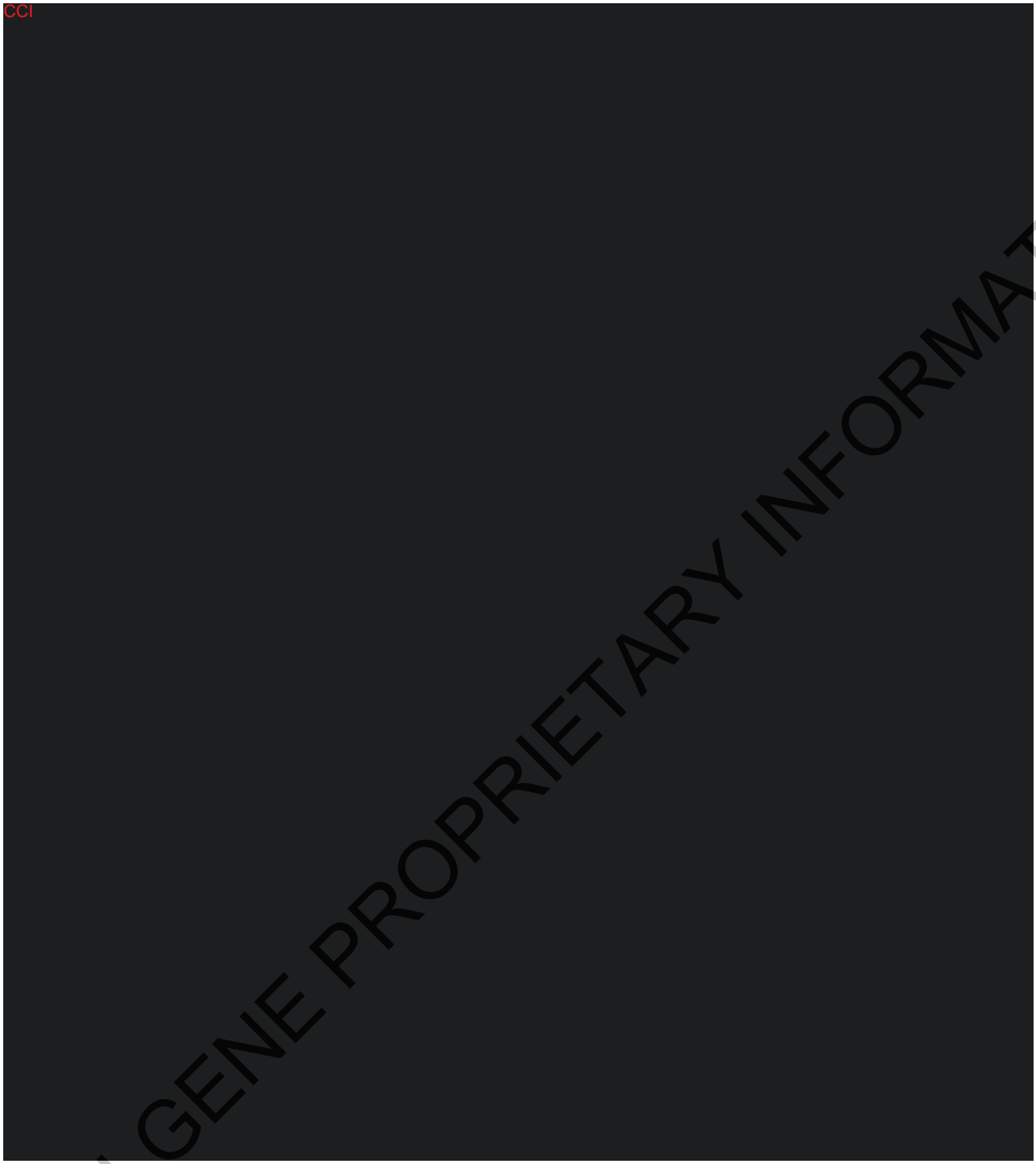

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APPENDIX K. MEDICATIONS THAT INHIBIT CYP3A4

Compound (Brand Names)
Azole Antifungals
Ketoconazole (Nizoral, Ketozole)
Itraconazole (Sporanox)
Fluconazole (Diflucan)
HIV Protease Inhibitors
Ritonavir (Norvir, Kaletra)
Indinavir (Crixivan)
Saquinavir (Invirase, Fortovase)
Nelfinavir (Viracept)
Macrolide Antibiotics
Erythromycin (Benzamycin, Eyrc, E-glades, Erygel, E-solve 2, Akne-Mycin, Eryderm, Sansac, Erythro-Statin, Erymax, Staticin, T-Stat, C-solve-2, Erycetter, PCE, Ery-Tab, E-Mycin, E-Base, E.E.S., Eryped, E.E.S 200, E.E.S 400, Pediamycin, Eryzole, Erythrocin)
Clarithromycin (Prevpac, Biaxin)
Telithromycin
Serotonin Reuptake Inhibitors (SSRI's)
Nefazodone (Serzone)
Fluvoxamine (Luvox)
Antiemetics
Aprepitant (Emend)
Antihypertensives
Diltiazem (Taztia, Cartia, Cardizem, Dilt-CD, Dilacor, Teczem, Tiamate, Trizac)
Verapamil (Tarka, Verelan, Isoptin, Covera-HS, Calan)
Others
Grapefruit juice
Atazanavir

CYP3A Inducers

CYP Enzymes	Strong Inducers ≥ 80% decrease in AUC
CYP3A	Carbamazepine, phenytoin, rifampin, St. John's wort(herbal)

APPENDIX L. HEPATITIS EXCLUSION CRITERIA

Exclusion Criteria

- Subjects who meet any of the Hepatitis B criteria described in the table below are ineligible for the study.

HBsAg anti-HBc IgM anti-HBc anti-HBs	positive positive positive negative	Acutely infected
HBsAg anti-HBc IgM anti-HBc anti-HBs	positive positive negative negative	Chronically infected
HBsAg anti-HBc anti-HBs	negative positive negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. "Low level" chronic infection 4. Resolving acute infection

Source: Mast, 2005.

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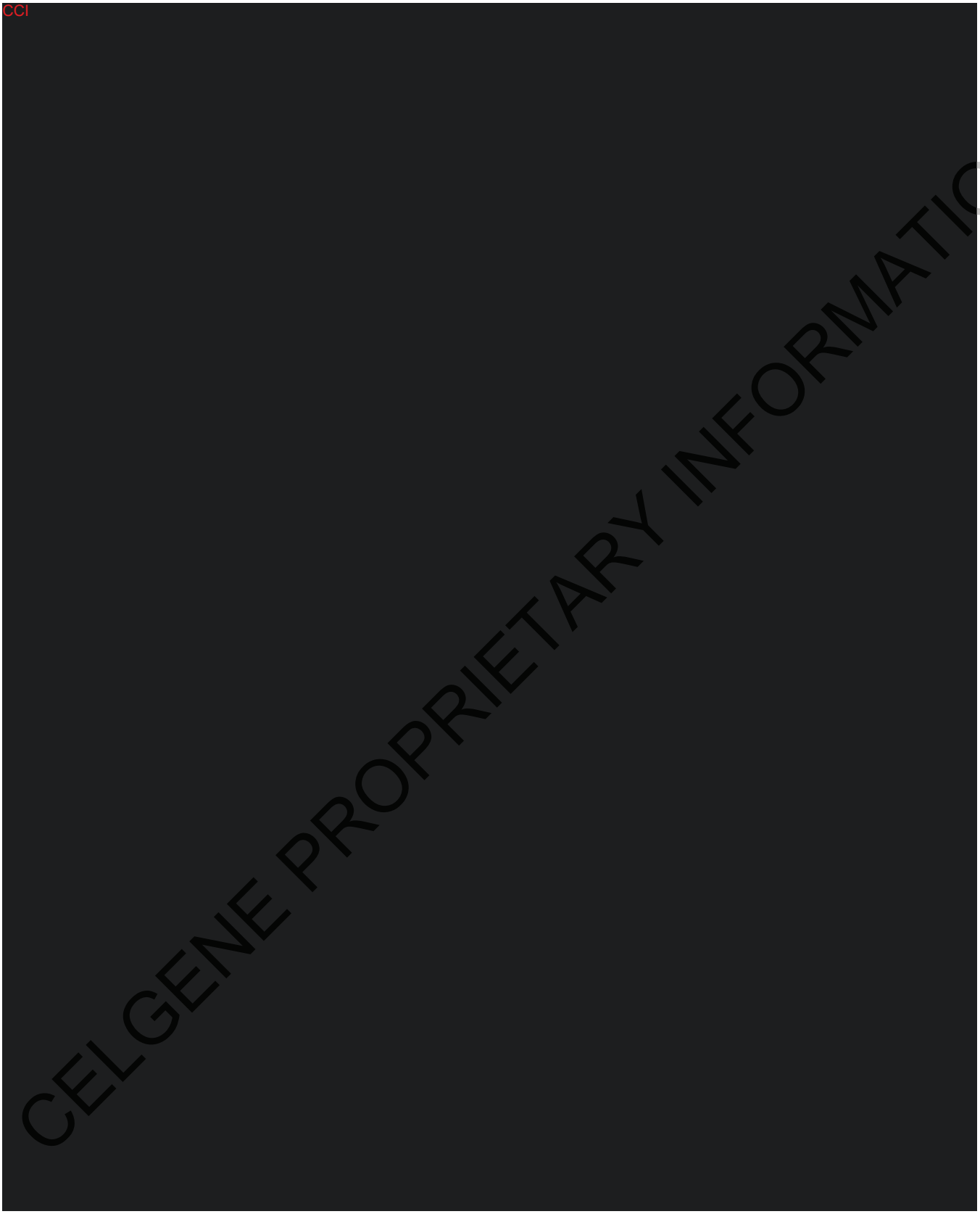

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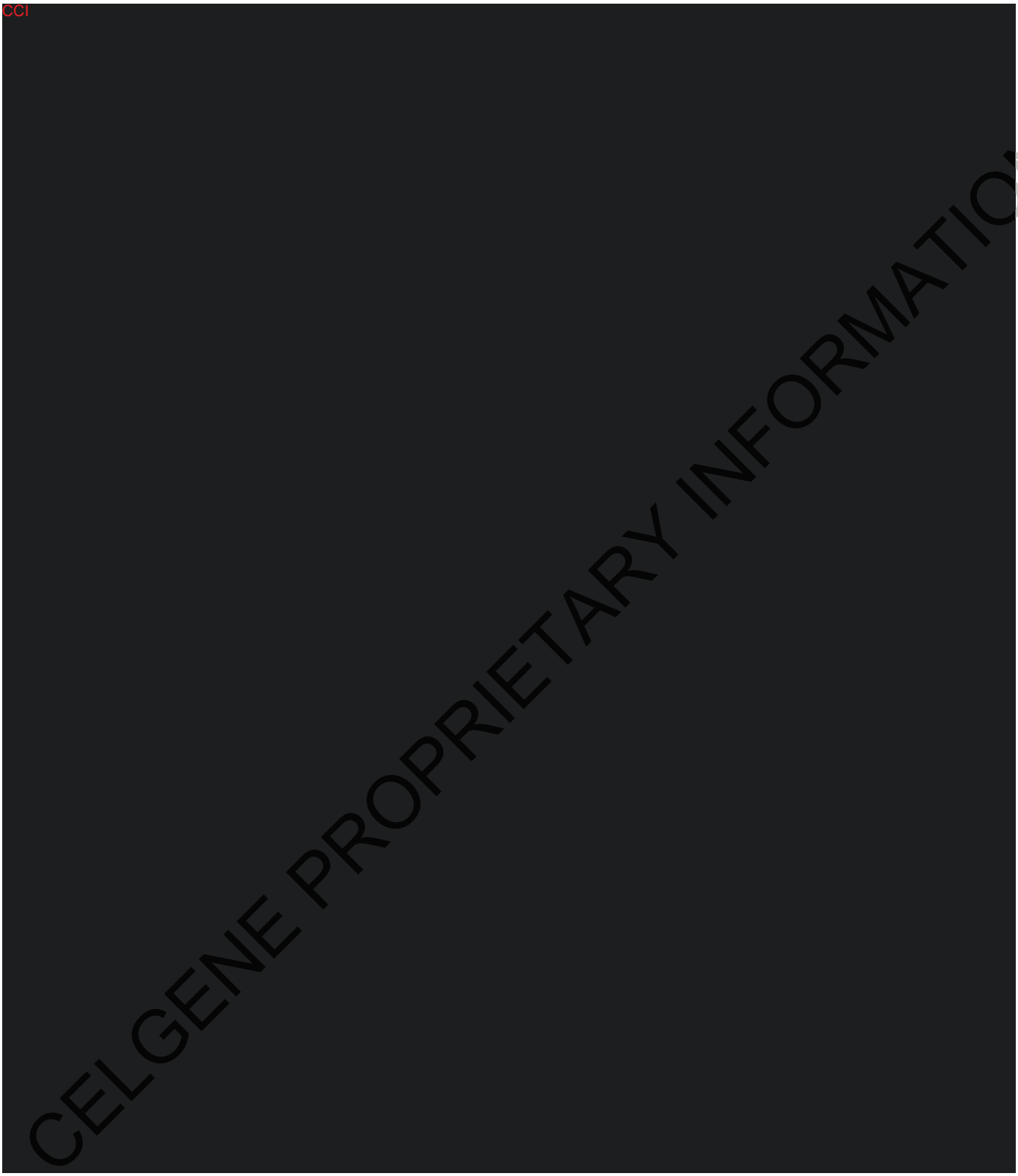

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APPENDIX O. SLICC/ACR SLE DAMAGE INDEX

SLICC/ACR SLE DAMAGE INDEX

Date of Assessment: (yy/mm/dd) ____ / ____ / _____

Damage occurring since diagnosis of lupus, ascertained by clinical assessment and present for at least 6 months unless otherwise stated. Repeat episodes mean at least 6 months apart to score 2. The same lesion cannot be scored twice.

ITEM	SCORE (circle)		
OCULAR (Either eye, by clinical assessment)			
Any cataract ever	0	1	
Retinal change OR optic atrophy	0	1	
NEUROPSYCHIATRIC			
Cognitive impairment (e.g., memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance level)	0	1	
OR Major psychosis	0	1	
Seizures requiring therapy for 6 months	0	1	2
Cerebral vascular accident ever (Score 2 if >1) OR resection not for malignancy	0	1	
Cranial or peripheral neuropathy (excluding optic)	0	1	
Transverse myelitis	0	1	
RENAL			
Estimated or measured GFR <50%	0	1	
Proteinuria 24 h, ≥ 3.5 g	0	1	
OR			
End-stage renal disease (regardless of dialysis or transplantation)		3	
PULMONARY			
Pulmonary hypertension (right ventricular prominence or loud P2)	0	1	
Pulmonary fibrosis (physical and X-ray)	0	1	
Shrinking lung (X-ray)	0	1	
Pleural fibrosis (X-ray)	0	1	
Pulmonary infarction (X-ray) OR resection not for malignancy	0	1	
CARDIOVASCULAR			
Angina OR coronary artery bypass	0	1	
Myocardial infarction ever (Score 2 if >1)	0	1	2
Cardiomyopathy (ventricular dysfunction)	0	1	
Valvular disease (diastolic murmur or a systolic murmur > 3/6)	0	1	
Pericarditis x 6 months or pericardiectomy	0	1	

APPENDIX O. SLICC/ACR SLE DAMAGE INDEX (Continued)

SLICC SLE DAMAGE INDEX - Page 2

PERIPHERAL VASCULAR	
Claudication x 6 months	0 1
Minor tissue loss (pulp space)	0 1
Significant tissue loss ever (e.g., loss of digit or limb, resection) (Score 2 if >1)	0 1 2
Venous thrombosis with swelling, ulceration, OR venous stasis	0 1
GASTROINTESTINAL	
Infarction or resection of bowel (below duodenum), spleen, liver, or gall bladder ever (Score 2 if >1)	0 1 2
Mesenteric insufficiency	0 1
Chronic peritonitis	0 1
Stricture OR upper gastrointestinal tract surgery ever	0 1
Pancreatic insuffiency requiring enzyme replacement or with pseudocyst	0 1
MUSCULOSKELETAL	
Atrophy or weakness	0 1
Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis)	0 1
Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	0 1
Avascular necrosis (Score 2 if >1)	0 1 2
Osteomyelitis	0 1
Ruptured tendons	0 1
SKIN	
Alopecia	0 1
Extensive scarring or panniculum other than scalp and pulp space	0 1
Skin ulceration (excluding thrombosis) for more than 6 months	0 1
PREMATURE GONADAL FAILURE	0 1
DIABETES (regardless of treatment)	0 1
MALIGNANCY (Exclude dysplasia)	0 1 2
TOTAL SCORE	

APPENDIX O. SLICC/ACR SLE DAMAGE INDEX (Continued)

INSTRUCTIONS / GLOSSARY

SLICC/ACR DAMAGE INDEX
GLOSSARY OF TERMS

Damage:	Non-reversible change, not related to active inflammation, occurring since diagnosis of lupus, ascertained by clinical assessment and present for at least 6 months unless otherwise stated. Repeat episodes mean at least 6 months apart to score 2. The same lesion cannot be scored twice.
Cataract:	A lens opacity (cataract) in either eye, ever, whether primary or secondary to steroid therapy, documented by ophthalmoscopy.
Retinal change:	Documented by ophthalmoscopic examination, may result in field defect, legal blindness.
Optic atrophy:	Documented by ophthalmoscopic examination.
Cognitive impairment:	Memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance level, documented on clinical examination or by formal neurocognitive testing.
Major psychosis:	Altered ability to function in normal activity due to psychiatric reasons. Severe disturbance in the perception of reality characterized by the following features: delusions, hallucinations (auditory, visual), incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behaviour.
Seizures:	Paroxysmal electrical discharge occurring in the brain and producing characteristic physical changes including tonic and clonic movements and certain behavioral disorders. Only seizures requiring therapy for 6 months are counted as damage.
CVA:	Cerebral vascular accident resulting in focal findings such as paresis, weakness, etc. OR surgical resection for causes other than malignancy.
Neuropathy:	Damage to either a cranial or peripheral nerve, excluding optic nerve, resulting in either motor or sensory dysfunction.
Transverse myelitis:	Lower extremity weakness or sensory loss with loss of rectal and urinary bladder sphincter control.
Renal:	Estimated or measured GFR <50%, proteinuria ≥ 3.5 g in 24 hours, or end-stage renal disease (regardless of dialysis or transplantation).
Pulmonary:	Pulmonary hypertension (right ventricular prominence or loud P2), pulmonary fibrosis (physical and X-ray), shrinking lung (X-ray), pleural fibrosis (X-ray), pulmonary infarction (X-ray), a resection for cause other than malignancy.
Cardiovascular:	Angina or coronary artery bypass, myocardial infarction (documented by EKG and enzymes) ever, cardiomyopathy (ventricular dysfunction documented clinically), valvular disease (diastolic murmur or a systolic murmur > 3/6), pericarditis X 6 months pericardiectomy.

Data Collection Protocol – Follow-up: Version #14, 31-MAY-2011

APPENDIX O. SLICC/ACR SLE DAMAGE INDEX (Continued)

INSTRUCTIONS / GLOSSARY

Peripheral Vascular:	Claudication, persistent for 6 months, by history. Minor tissue loss, such as pulp space, ever. Significant tissue loss, such as loss of digit or limb, or resection, ever. Venous thrombosis with swelling, ulceration, or clinical evidence of venous stasis.
Gastrointestinal:	Infarction or resection of bowel below duodenum, by history. Resection of spleen, liver, or gall-bladder ever, for whatever cause. Mesenteric insufficiency, with diffuse abdominal pain, on clinical examination. Chronic peritonitis, with persistent abdominal pain and peritoneal irritations, on clinical examination. Oesophageal stricture, shown on endoscopy. Upper gastrointestinal tract surgery, such as correction of stricture, ulcer surgery, etc., ever, by history. Pancreatic insufficiency requiring enzyme replacement or with a pseudocyst.
Musculoskeletal:	Muscle atrophy or weakness, demonstrated on clinical examination. Deforming or erosive arthritis, including reducible deformities (excluding avascular necrosis), on clinical examination. Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis) demonstrated n X-ray. Avascular necrosis, demonstrated on any imaging technique. Osteomyelitis, documented clinically, and supported by culture evidence. Tendon ruptures.
Skin:	Scarring, chronic alopecia, documented clinically. Extensive scarring or panniculum other than scalp and pulp space, documented clinically. Skin ulceration (excluding thrombosis) for more than 6 months.
Premature Gonadal Failure:	Secondary amenorrhea, prior to age 40.
Diabetes:	Diabetes requiring therapy but regardless of treatment.
Malignancy:	Documented by pathology, excluding dysplasias.

Data Collection Protocol – Follow-up: Version #14, 31-MAY-2011

APPENDIX P. BRITISH ISLE LUPUS ASSESSMENT GROUP 2004

Date of Assessment: **Date of Birth:** **Name/ID:**

BILAG2004 INDEX ASSESSMENT

Only features attributable to SLE are to be recorded and refer to the last 4 weeks compared with the previous 4 weeks.

Scoring for features: **1 Improving**
2 Same
3 Worse
4 New
Yes/No (where indicated)
value (where indicated)
❑ indicat e if f eature not due to lupus
(default is 0 = not present)

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

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

NEUROPSYCHIATRIC
19. Aseptic meningitis ( )
20. Cerebral vasculitis ( )
21. Demyelinating syndrome ( )
22. Myelopathy ( )
23. Acute confusional state ( )
24. Psychosis ( )
25. Acute inflammatory demyelinating polyradiculoneuropathy ( )
26. Mononeuropathy (single/multiplex) ( )
27. Cranial neuropathy ( )
28. Plexopathy ( )
29. Polyneuropathy ( )
30. Seizure disorder ( )
31. Status epilepticus ( )
32. Cerebrovascular disease (not due to vasculitis) ( )
33. Cognitive dysfunction ( )
34. Movement disorder ( )
35. Autonomic disorder ( )
36. Cerebellar ataxia ( )
37. Headache, severe, unremitting ( )
38. Migraine with/without aura ( )
39. Tension headache ( )
40. Cluster headache ( )
41. Headache from IC hypertension ( )
42. Mood disorder (depression/mania) ( )
43. Anxiety disorder ( )

MUSCULOSKELETAL
44. Definite myositis (Bohan & Peter) ( )
45. Myositis with incomplete criteria ( )
46. Severe polyarthritis ( )
47. Arthritis/Tendonitis ( )
48. Arthralgia/Myalgia ( )

Revision: 12/Apr/2004

CARDIORESPIRATORY
49. Myocarditis - mild ( )
50. Cardiac failure ( )
51. Arrhythmia ( )
52. New valvular dysfunction ( )
53. Serositis (pleuro-pericardial pain) - mild ( )
54. Cardiac tamponade ( )
55. Pleural effusion with dyspnoea ( )
56. Pulmonary haemorrhage/vasculitis ( )
57. Interstitial alveolitis/pneumonitis ( )
58. Shrinking lung syndrome ( )
59. Aortitis ( )
60. Coronary vasculitis ( )

GASTROINTESTINAL
61. Peritonitis ( )
62. Abdominal serositis or ascites ( )
63. Lupus enteritis/colitis ( )
64. Malabsorption ( )
65. Protein losing enteropathy ( )
66. Intestinal pseudo-obstruction ( )
67. Hepatitis ( )
68. Acute cholecystitis ( )
69. Acute pancreatitis ( )

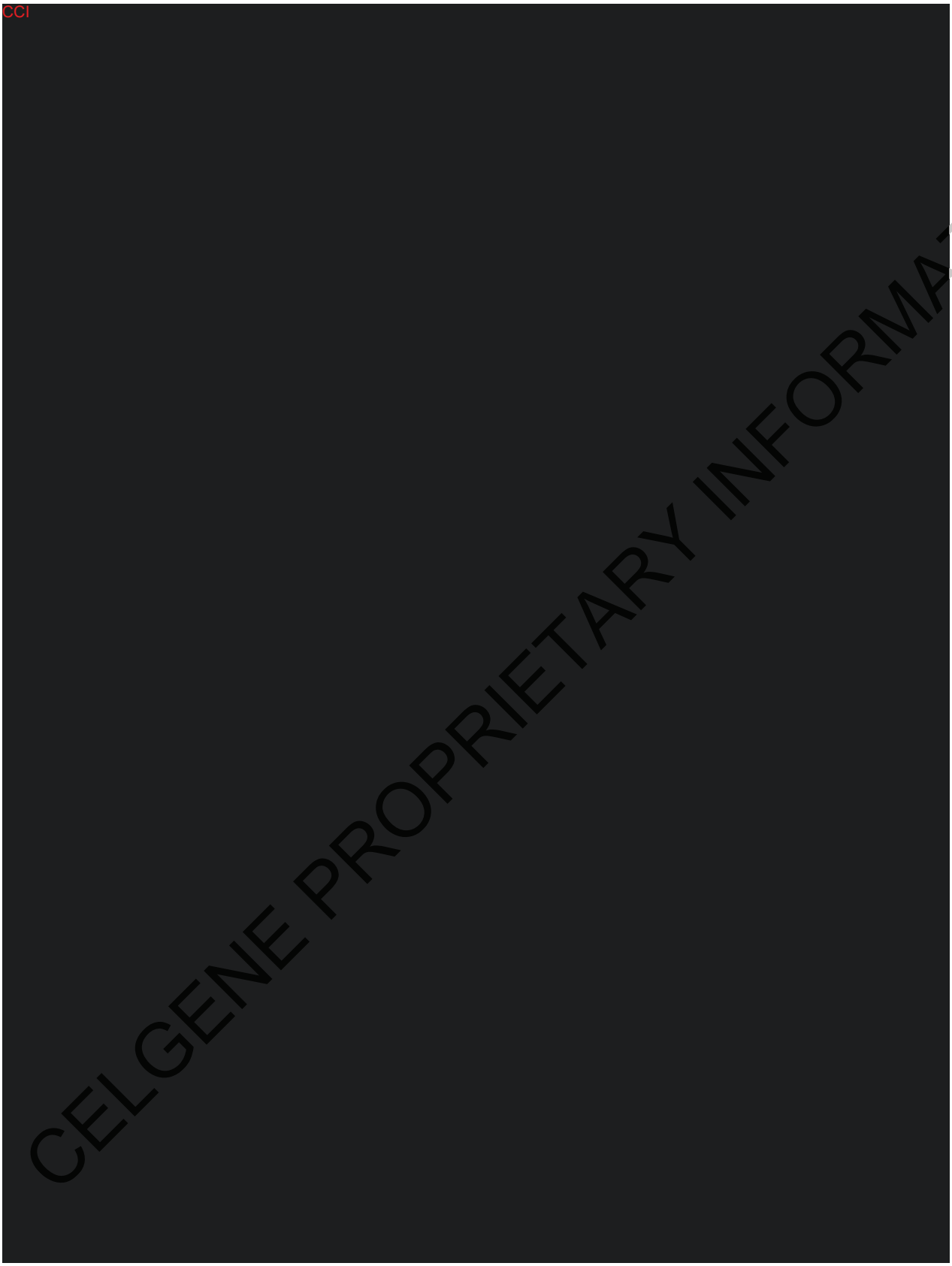
OPHTHALMIC
70. Orbital inflammation with myositis and/or extra ocular muscle swelling and/or proptosis ( )
71. Keratitis - severe ( )
72. Keratitis - mild ( )
73. Anterior uveitis ( )
74. Posterior uveitis/retinal vasculitis - severe ( )
75. Posterior uveitis/retinal vasculitis - mild ( )
76. Episcleritis ( )
77. Scleritis - severe ( )
78. Scleritis - mild ( )
79. Retinal/choroidal vaso-occlusive disease ( )
80. Isolated cotton-wool spots (cytoid bodies) ( )
81. Optic neuritis ( )
82. Anterior ischaemic optic neuropathy ( )

RENAL
83. Systolic blood pressure (mm Hg) value ( ) ❑
84. Diastolic blood pressure (mm Hg) value ( ) ❑
85. Accelerated hypertension Yes/No ( ) ❑
86. Urine dipstick (-=0,+=1, ++=2, +++=3) ( ) ❑
87. Urine albumin-creatinine ratio mg/mmol ( ) ❑
88. Urine protein-creatinine ratio mg/mmol ( ) ❑
89. 24 hour urine protein (g) value ( ) ❑
90. Nephrotic syndrome Yes/No ( ) ❑
91. Creatinine (plasma/serum) µmol/l ( ) ❑
92. GFR (calculated) ml/min ( ) ❑
93. Active urinary sediment Yes/No ( )
94. Histological evidence of active nephritis (within 3 months) (Yes/No) ( )

HAEMATOLOGY
95. Haemoglobin (g/dl) value ( ) ❑
96. Total white cell count (x 10^9/l) value ( ) ❑
97. Neutrophils (x 10^9/l) value ( ) ❑
98. Lymphocytes (x 10^9/l) value ( ) ❑
99. Platelets (x 10^9/l) value ( ) ❑
100. Evidence of active haemolysis Yes/No ( )
101. Coombs' test positive (isolated) Yes/No ( )

Weight (kg):	**Serum urea (mmol/l):**
Black (Yes/No):	**Serum albumin (g/dl):**

CCI



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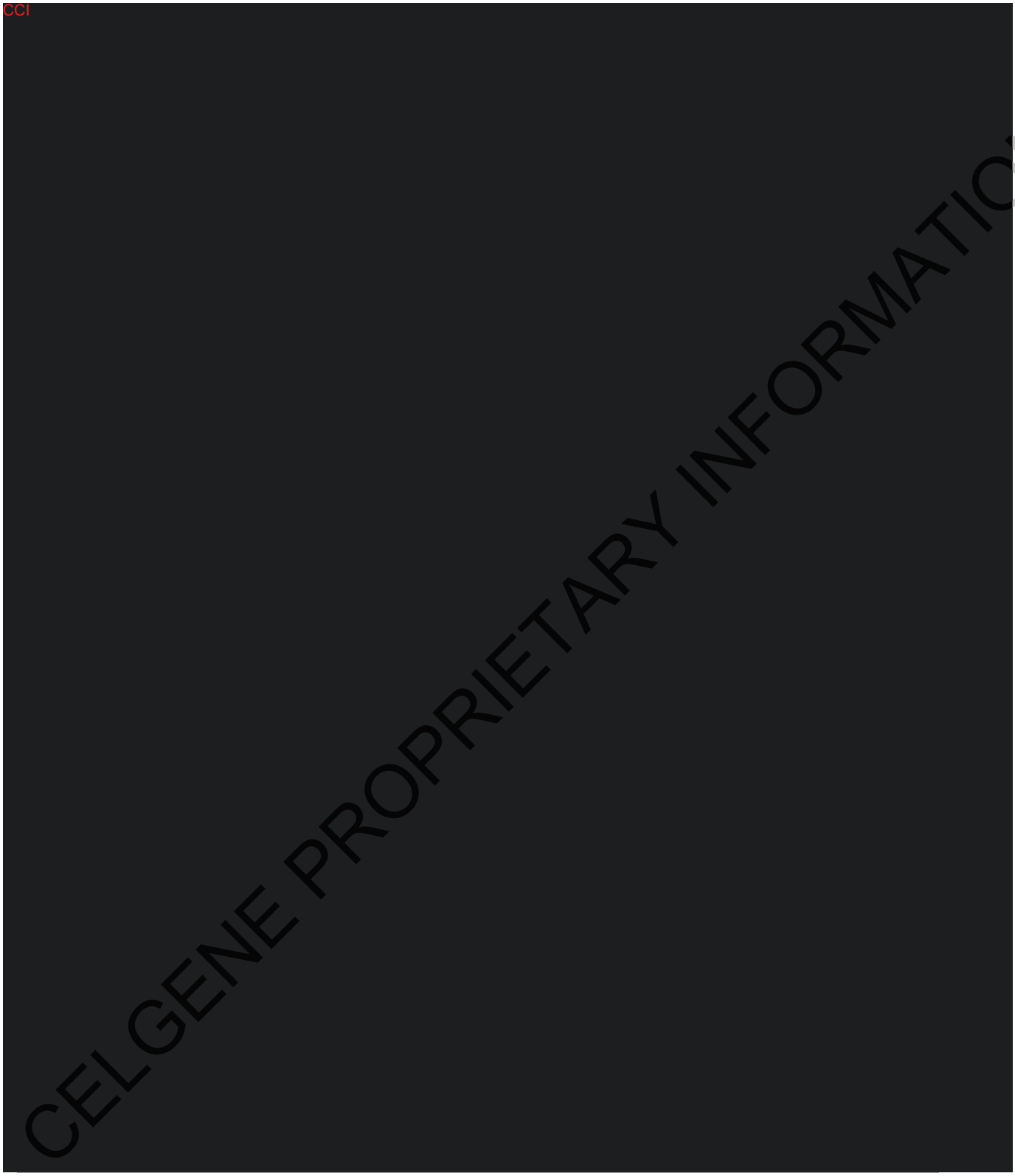

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Celgene Signing Page

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UserName: PPD
Title: PPD
Date: Wednesday, 20 June 2018, 03:33 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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1. JUSTIFICATION FOR AMENDMENT

Protocol Amendment 6 contains changes to the study [redacted] regarding thromboembolic risk and prophylaxis.

Key changes to the protocol included in this amendment are summarized below.

- **Update the thromboprophylaxis requirements and recommendations**

The thromboprophylaxis requirements for study participation were updated as follows:

- The use of aspirin was changed from recommended to mandatory use of thromboprophylaxis with low dose aspirin, low molecular weight heparin or other equivalent antithrombotic or anticoagulant unless the investigator determines that, based on the totality of the subjects' risk factors for thrombosis, thromboprophylaxis is not required or is contraindicated.

- If any additional prophylaxis is needed, it should be based on the local standard of care and the investigator's best judgement after careful consideration of the benefit versus the potential risk for the individual subject.

Subjects with lupus are already at an increased risk for thromboembolism from their disease and other potential underlying factors. The investigator will be prompted to carefully evaluate the risk/benefit for subject's participation in the study based on the totality of thromboembolic risk factors (antiphospholipid status, hormonal contraceptives, corticosteroids, smoking, obesity, immobilization, etc.) in addition to CC-220 exposure.

These changes were implemented to help mitigate the increased risk of thromboembolic events observed with the class of medications which CC-220 belongs to, in subjects with lupus.

Revised Sections: Protocol Summary, Section 4.1 Study Design, Section 4.2.5 Concomitant Medications, Section 4.2.7 Safety, Section 9.1 Permitted Concomitant Medications and Procedures, Section 9.3 Required Concomitant Medications and Procedures

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

Removal of Part 2

Based on Amendment 5, Part 2 of the CC-220-SLE-001 protocol will not be conducted. All references to Part 2 of the study in this protocol are no longer applicable, so they have been removed.

Rather than conduct Part 2, the decision was made by the Sponsor to conduct this part of the study under a separate "stand-alone" Phase 2B protocol. The decision to create a separate protocol was made due to modifications in the targeted study population, the sample size, and the CC-220 doses being tested. A separate protocol will allow for greater operational efficiency as the study is expanded to new countries/sites and provide greater clarity to the study design. The decision to separate Part 2 from CC-220-SLE-001 was not based on any safety concerns.

Revised Sections:

- Part 2 was pervasive throughout the protocol – nearly every section has been modified.

Removal of the 0.6 mg once daily (QD) dose from the Active Treatment Extension Phase (ATEP)

Data from the now completed Part 1 of CC-220-SLE-001 has revealed that there was a significant increase in plasma cells and a trend for increasing CD4 and CD8 T cells in subjects receiving the 0.6 mg QD dose. Additionally, Grade 3 neutropenia and dermatitis were observed with the 0.6 mg QD dose. Based upon this information it was decided that this is not a dose the Sponsor will pursue in the exploration of CC-220 in systemic lupus erythematosus (SLE). As a result, any subject enrolled in the ATEP on the 0.6 mg QD dose will be dose reduced to the 0.6 mg/0.3 mg on alternating days dose upon the implementation of this amendment. Subjects in the ATEP taking 0.3 mg QD and 0.6/0.3 mg QD on alternating days should continue their investigational product (IP), as these doses were shown to reduce key SLE cytokines with a less pronounced side effect profile. It should be noted that this mandatory reduction in dose does **not** count as the dose reduction afforded to each subject one time during the ATEP.

Revised Sections:

- Protocol Summary
- Section 4.1, Study Design
- Section 4.2.3, Dose and Dose Interval
- Section 8.2.1, Dose Modification or Interruption
- Section 12.1, Subject Stopping Rules

Addition of an Early Termination Visit to the ATEP

Amendment 4 of the protocol failed to include an Early Termination Visit for the ATEP portion of the protocol. As it is important to capture key efficacy and safety measures for subjects who stop the ATEP early, a mechanism to capture these data was added. This amendment has added

an Early Termination Visit to the ATEP to provide sites with a specific set of assessments that will be captured for all subjects who do not complete the ATEP.

Revised Sections:

- Protocol Summary
- Section 4.1, Study Design
- Section 5, Table of Events, Table 2

Clarification of adverse event (AE) collection duration following cessation of IP for the ATEP

Amendment 4 of the protocol specified that AEs should be recorded for 84 days following cessation of study drug. This was appropriate for Part 1 of the study given the 84-day Observational Follow-up Phase. However, the ATEP only has a 28-day Observational Follow-up Phase so the protocol was updated to specify that AEs should only be recorded up to 28 days following cessation of study drug for those subjects in the ATEP.

Revised Sections:

- Section 11.1, Monitoring, Recording and Reporting of Adverse Events
- Section 11.5, Reporting of Serious Adverse Events

PRN (as needed) and stable use of non-steroidal anti-inflammatory drugs (NSAIDs)

Up through Amendment 4 of the protocol, only PRN use of NSAIDs was addressed. During the ATEP, many sites have sought clarification of how to treat PRN versus stable use of NSAIDs – specifically with regard to whether both groups of these NSAID users should stop NSAID treatment 12 hours prior to study visits. In order to clarify that subjects on a stable dose of NSAIDs **or** NSAIDs PRN must stop their medication 12 hours prior to a study visit, the protocol was modified to indicate that any NSAID use requires cessation 12 hours prior to a study visit.

Revised Sections:

- Protocol Summary
- Section 4.1, Study Design
- Section 4.2.5, Concomitant Medications
- Section 9.1, Permitted Concomitant Medications and Procedures

Updated CC-220 study information

Additional CC-220 information obtained since the last protocol amendment was added to provide the most current information for ongoing and completed studies using CC-220.

Revised Sections:

- Section 1, Introduction

Clarification of ATEP enrollment closure

Protocol Amendment 4 imposed no time restriction between when a subject completed Part 1 and when they entered into the ATEP. For the current amendment, language was inserted to

clarify that no additional subjects would be permitted to enter the ATEP upon implementation of Protocol Amendment 5.

Revised Sections:

- Protocol Summary
- Section 4.1, Study Design

CCI [redacted]

Clarification of permitted concomitant medications

Many of the study sites queried the medical monitor about use of topical steroids and ophthalmologic cyclosporine during the ATEP. As a result, clarification language was added to specify what was permitted and what was excluded during treatment in the ATEP.

Revised Sections:

- Section 7.2.2, Inclusion Criteria, Active Treatment Extension Phase
- Section 7.3.1, Exclusion Criteria, Part 1 and Active Treatment Extension Phase
- Section 9.1, Permitted Concomitant Medications and Procedures

Clarification of overdose language

Based upon discussions during the development of the subsequent CC-220 SLE protocol, the overdose language was modified to be consistent across CC-220 studies.

Revised Sections:

- Section 8.2.2, Overdose

Duration of birth control after cessation of study drug in male subjects

Based upon recommendation from nonclinical colleagues, modification of the duration male subjects must agree to abstinence or condom use following cessation of study drug was extended to 90 days.

Revised Sections:

- Sections 7.2.1 and 7.2.2, Inclusion Criteria

Pregnancy testing for females of child bearing potential (FCBPs) with irregular or no menses during the ATEP

Language was modified to clarify that FCBPs with irregular or no menses during the ATEP should have pregnancy testing every 14 days while on study, at treatment discontinuation and at 14 and 28 days following treatment discontinuation.

Revised Sections:

- Sections 7.2.1 and 7.2.2, Inclusion Criteria

Clarification of birth control language following cessation of study drug

Based upon recommendation from nonclinical colleagues, modification of the duration male subjects must agree to abstinence or condom use following cessation of study drug was extended to 90 days.

Revised Sections:

- Sections 7.2.1 and 7.2.2, Inclusion Criteria

Removal of Pharmacogenetic Assessments

As pharmacogenetic assessment was only included in the Part 2 of the original CC-220-SLE-001 protocol, no pharmacogenetics analyses will be conducted in this protocol.

Revised Sections:

- Part 2 was pervasive throughout the protocol – every section which mentioned the pharmacogenetic component of the study has been removed.

Minor changes have been made throughout the document for clarity and consistency.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- A new medical monitor was put onto the study so the medical monitor information was updated.

  Revised section: MEDICAL MONITOR/EMERGENCY CONTACT INFORMATION

- The primary reason for amending the protocol was to add an active treatment extension phase (ATEP) to allow subjects who were deriving benefit from CC-220 in either Part 1 or Part 2 of the core study to continue to receive treatment for up to an additional 2 years. The following changes have been made to make accommodations for this added study phase:
  - The addition of the ATEP to the study required that additional objectives were specified for the newly added study phase

    Revised sections: PROTOCOL SUMMARY: Objectives
  - The Study Design Section of the PROTOCOL SUMMARY was amended to define the new ATEP and detail how it will interact with the currently ongoing core study (Part 1 and Part 2).
    - The study now features 3 parts (Part 1, Part 2 and ATEP) instead of 2 parts
    - For subjects completing Part 1 or Part 2 of the study who elect to enter the ATEP, the Observation Follow-Up Phase will be delayed until the conclusion of their involvement with the ATEP.
    - A detailed description of the ATEP and the logistics of how subjects completing Part 1 or Part 2 of the core study can enter the ATEP were added to the PROTOCOL SUMMARY.
    - An expanded list of concomitant medications will be permitted for subjects participating in the ATEP. This added flexibility with concomitant medication was added to accommodate for potential changes in treatment during the extended two-year period of study involvement.
    - An explanation of the rules for dose reduction and/or interruption for subjects in the ATEP was added.

    Revised sections: PROTOCOL SUMMARY: Study Design
  - The Study Population Section of the PROTOCOL SUMMARY was modified to define the population for the newly added ATEP.

    Revised sections: PROTOCOL SUMMARY: Study Population
  - The Length of Study Section of the PROTOCOL SUMMARY was modified to incorporate the ATEP duration.

    Revised sections: PROTOCOL SUMMARY: Length of Study

- The Study Treatments Section of the PROTOCOL SUMMARY was modified to include the dosing paradigm for the ATEP. It details how there will be no placebo or 0.3 mg every other day (QOD) dosing in the ATEP.

  Revised sections: PROTOCOL SUMMARY: Study Treatments

- Additional vaccine titer monitoring was added to the protocol to assess for the potential attenuation of vaccine effectiveness due to CC-220. In addition, to tetanus, both pneumococcal and influenza titers were added.

  Revised sections: PROTOCOL SUMMARY: Overview of Safety Assessments

- Analysis of amylase was added to the safety assessments in order to enhance (lipase already being measured for pancreatic function) monitoring for any changes in pancreatic function of the subjects on CC-220.

  Revised sections: PROTOCOL SUMMARY: Overview of Safety Assessments

- Language added to specify that ATEP will not include any pharmacokinetics (PK), pharmacogenetics (PG) or pharmacodynamics (PD) analyses.

  Revised sections: PROTOCOL SUMMARY: Overview of Pharmacokinetic, Pharmacogenetic, and Pharmacodynamic Assessments

- CCI [redacted]

  Revised sections: PROTOCOL SUMMARY: CCI [redacted]

- Additional information regarding animal data not available at the time of the last amendment was added to the Introduction Section of the protocol.

  Revised sections: Section 1 Introduction

- CCI [redacted]

  Revised sections: Section 2.3 ATEP

- The addition of the ATEP to the study required that additional endpoints were specified for the newly added study phase.

  Revised sections: Section 3.3 ATEP

- Modifications to the study design and study population section of the protocol (Section 4) mirror those made to the PROTOCOL SUMMARY study design and study population section detailed above.

Revised sections: Section 4.1 Study Design and Section 4.2 Study Design Rationale

- Modifications to the duration of treatment section of the protocol were made to add the ATEP.

  Revised sections: 4.2.1 Duration of Treatment

- Language stating that the ATEP would not be blinded was added.

  Revised sections: 4.2.4 Blinding

- Additional concomitant medications will be permitted for subjects enrolled into the ATEP (as described in the PROTOCOL SUMMARY changes detailed above). In addition, the recommendation of anti-platelet or anti-coagulation use was expanded beyond just those subjects with a history of thromboembolic events to all subjects. This modification was implemented based upon the recommendation by the safety review team responsible for monitoring the safety of CC-220 in this trial.

  Revised sections: Section 4.2.5 Concomitant Medications

- Additional titers for monitoring of attenuation of vaccines while on CC-220 and amylase for the monitoring of pancreatic function (as indicated above in the PROTOCOL SUMMARY) were added to Safety Section of the protocol.

  Revised sections: Section 4.2.7 Safety

- The original study schematic was modified to include the newly added ATEP.

  Revised sections: Figure 1 Overall Study Design

- The study duration was modified based upon the newly added ATEP (same as described above in the PROTOCOL SUMMARY and Section 4.2.1 Duration of Treatment).

  Revised sections: Section 4.3 Study Duration

- Additional footnotes were added to the Schedule of Assessments for Part 1 and Part 2 of the study detailing study drug dispensation and logistics surrounding who and when subjects will enter the Observational Follow-Up Phase depending on their participation in the ATEP.

  Revised sections: Table 1: Part 1 and Table 2: Part 2

- A Schedule of Assessments Table was added to detail the visit structure, assessments, and assessment schedule for the newly added ATEP.

  Revised sections: Table 3: ATEP

- The Study Entry section was updated with inclusion of an Informed Consent Document (ICD) for the ATEP. The safety assessments section was modified to include a measure of weight and waist circumference during all complete physical assessments to monitor for obesity in the study subjects in the ATEP. Information on additional vaccine titers, amylase testing and frequency of hormone testing in the ATEP was also added to this section. The rationale for additional titers and

amylase testing have been explained above. The information specifying the frequency of hormone testing was added as this monitoring will be at different intervals during the ATEP versus Part 1 or Part 2 of the study.

Revised sections: Section 6: Procedures: Study Entry and Safety Assessments

- The BILAG 2004 assessment was added to the battery of efficacy assessments planned for the subjects participating in the ATEP. As stated above, this instrument was added to provide us with additional information on how CC-220 is impacting the lupus population.

  Revised sections: Section 6: Procedures: Efficacy Assessments

- CCI [redacted]

- The study population section was modified to incorporate the newly added ATEP.

  Revised sections: Section 7.1: Number of Subjects and Sites

- Instructions with regard to inclusion criteria for subjects entering the ATEP was added. In addition, clarification regarding use of the SELENA Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) for inclusion was added. Sites will be permitted to use non-lab components of the SELENA SLEDAI to qualify patients for enrollment in the event that the laboratory results associated with the SELENA SLEDAI have not been received.

  Revised sections: Section 7.2 Inclusion Criteria, 7.2.3: ATEP

- Instructions with regard to exclusion criteria for subjects entering the ATEP were added. In addition, the exclusion criterion for the minimum allowable platelet count was lowered to allow for greater flexibility for study entry.

  Revised sections: Section 7.3.1: Part 1, Part 2 and ATEP

- Instructions with regard to dose modification or interruption for subjects participating in the ATEP were added.

  Revised sections: Section 8.2.1: Dose Modification or Interruption

- Information regarding additional permitted concomitant medication for subjects participating in the ATEP was added.

  Revised sections: Section 9.1: Permitted Concomitant Medications and Procedures

- Additional information was added to detail statistical analyses to be conducted for subjects participating the ATEP.

Revised sections: Section 10.1: Overview, Section 10.6: Efficacy Analysis, and Section 10.8: Interim Analysis

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- To allow for greater enrollment flexibility, the following modifications were made to the protocol:
    - The entrance criterion dictating a minimum immunoglobulin M (IgM) level was removed from the protocol

      Revised Sections: Section 6 Procedures; Section 7.3 Exclusion Criteria
    - The timeframe of systemic lupus erythematosus (SLE) diagnosis per ACR Revised Criteria was modified to include past as well as present fulfillment of 4 of the 11 criteria required

      Revised Section: Section 7.2 Inclusion Criteria
    - Dose levels of antimalarials (hydroxychloroquine, chloroquine, or quinacine) permitted during the study were made less restrictive

      Revised Sections: Protocol Summary; Section 4.1 Study Design; Section 4.2.5 Concomitant Medications; Section 7.2 Inclusion Criteria; Section 9.1 Permitted Concomitant Medications and Procedures
    - Cyclophosphamide washout duration shortened by one month

      Revised Section: Section 7.3.1 Exclusion Criteria
    - The definition of unstable lupus nephritis was made less restrictive through a decrease in estimated glomerular filtration rate (eGFR) and removal of the exclusion based on proteinuria

      Revised Section: Section 7.3 Exclusion Criteria
    - The time by which subjects are required to taper to 10 mg of oral corticosteroids or less was moved from screening to randomization

      Revised Section: Section 7.2 Inclusion Criteria
    - The time required for subjects to withdraw from concomitant medications and procedures (from 8 weeks to 4 weeks for azathioprine and mycophenalate mofetil; from 12 to 6 months for rituximab or anti-CD22 therapy) was reduced by half

      Revised Section: Section 7.3 Exclusion Criteria
    - IgA and IgG testing was moved from Baseline to Screening in Table 1 Part 1 and Table 2 Part 2 of the Table of Events.

      Revised Section: Section 5 Table of Events, Table 1 and Table 2
    - The screening period was extended 2 weeks to a total of 6 weeks to allow subjects more flexibility for laboratory retesting in order to reduce the potential for screen failure

Revised Sections: Protocol Summary; Section 4.1 Study Design; Section 4.2.1 Duration of Treatment; Section 4.2 Study Design Rationale, Figure 1; Section 4.3 Study Duration; Section 5 Table of Events, Table 1 and Table 2; Section 7.2 Inclusion Criteria; Section 7.3 Exclusion Criteria

- The site personnel permitted to conduct safety and efficacy assessments during the study was clarified

  Revised Sections: Protocol Summary; Section 6 Procedures

- Clarification regarding use of inhaled and topical corticosteroids was added

  Revised Sections: Protocol Summary, Section 4.1 Study Design; Section 4.2.5 Concomitant Medications; Section 9.1 Permitted Concomitant Medications and Procedures

- Description of the ophthalmological exams was added to provide greater clarity

  Revised Sections: Protocol Summary; Section 6 Procedures

- Subject stopping rules and dose group stopping rules were modified to provide greater clarity

  Revised Sections: Section 12.1 Subject Stopping Rules; Section 12.2 Dose Group Stopping Rules

- CCI [redacted]

  Revised Sections: Protocol Summary; Section 1 Introduction; Section 4.2.7 Safety; Section 5 Table of Events, Table 1 and Table 2; Section 6 Procedures; Section 7.2 Inclusion Criteria

- Protocol was modified to allow all electrocardiograms (ECGs) from Visit 2 onward to be measured ≤ 15 minutes apart versus the original duration of only ≤ 5 minutes

  Revised Sections: Section 6 Procedures

- Pregnancy language was revised by safety

  Revised Section: 11.4 Pregnancy

- Modifications were made to the standard language defining investigator responsibilities

  Revised Section: 14.2 Investigator Responsibilities

- Appendix M Pregnancy Prevention Risk Management Plans was deleted

  Revised Sections: Appendix M; Section 5 Table of Events, Table 1 and Table 2; Section 7.2 Inclusion Criteria

- CCI [redacted]

- Additional language was added to Inclusion Criterion 10 for Part 1 and Inclusion Criterion 13 for Part 2. The additional language specifies that pregnancy counseling will be administered as described in the Pregnancy Prevention Plan.

  Revised Section: Section 7.2.1 Part 1, Section 7.2.2 Part 2

- Under laboratories which require repeated testing with 7 days, the percentage of eosinophilia was modified to be > 7%. This was done to reduce the amount of unnecessary alerts based on potential seasonal and/or perennial allergies.

  Revised section: Section 12.1 Subject Stopping Rules

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- A minimum Hybrid SELENA SLEDAI score was added to the inclusion criteria for both Part 1 and Part 2 to ensure that subjects coming into the study have a minimum level of active disease.
- The requirement to discontinue subjects based upon an increase in the Hybrid SELENA SLEDAI score was removed, as it has been determined that such a restrictive requirement will result in a disproportionate number of subject discontinuations.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- Antineutrophil cytoplasmic antibodies (ANCA), cell bound complement activated products (CB-CAPs) and B2 Glycoprotein 1 IgG/IgM laboratory assessments have been removed from the protocol in order to streamline laboratory assessments in the study.
- The SLICC/ACR SLE Damage Index was added to the protocol to explore the impact CC-220 has on the mitigation of damage to various organ systems resulting from SLE.
- Hepatitis B viral DNA by PCR testing has been removed as specific antibody results (indicating chronic versus acute infection) will not be required for this study.
- A more comprehensive description of the PG portion of the protocol was added to the protocol in order to clarify the intent of this substudy.
- To allow for greater enrollment flexibility, up to 2 rescreens instead of a single rescreen will now be permitted per protocol.
- Editorial changes have also been made to sections throughout the protocol to enhance clarity.