DISCLOSURE

REDACTED STATISTICAL ANALYSIS PLAN

CC-220-SLE-001 – Part 1

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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STATISTICAL ANALYSIS PLAN

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

STUDY DRUG: **CC-220**

PROTOCOL NUMBER: **CC-220-SLE-001 – Part 1**

DATE FINAL: **25Jul2016**

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On behalf of

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PROTOCOL TITLE	A PILOT, PHASE 2, RANDOMIZED, PLACEBOCONTROLLED, DOUBLE-BLIND, STUDY TO EVALUATE EFFICACY, SAFETY, TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS AND PHARMACOGENETICS OF CC-220 IN SUBJECTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS
INVESTIGATIONAL PRODUCT	CC-220
PROTOCOL NUMBER	CC-220-SLE-001
PROTOCOL VERSION, DATE	Amendment 4, 05-Jan2016
SIGNATURE STATEMENT	By my signature, I indicate I have reviewed this SAP and find its contents to be acceptable.

Statistical Therapeutic Area Head

Signature _____

Printed Name _____ Date _____

Lead Statistician

Signature PPD _____

Printed Name PPD _____ Date _____

Lead Clinical Research Physician / Clinical Research Physician PPD

Signature PPD _____

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Lead Product Safety Physician

Signature PPD _____

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Printed Name PPD Date PPD

Lead Statistician

Signature PPD

Printed Name PPD Date _____

Lead Clinical Research Physician / Clinical Research Physician

Signature _____

Printed Name _____ Date _____

Lead Product Safety Physician

Signature _____

Printed Name Date

1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

Abbreviation	Description
ACR	American College of Rheumatology
ADaM	Analysis Dataset Model
AE	Adverse event
ALT	Alanine aminotransferase/ serum glutamic-pyruvic transaminase (SGPT)
CCI	[redacted]
AST	Aspartate aminotransferase/ serum glutamic-oxaloacetic transaminase (SGOT)
ATC	Anatomical Therapeutical Chemical
BMI	Body mass index
BQL	Below the quantifiable limit
CI	Confidence interval
CLASI	Cutaneous Lupus Area and Severity Index
CRP	C-reactive protein
CV	Coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ESR	Erythrocyte sedimentation rate
GeoCV	Geometric coefficient of variation
Hgb	Hemoglobin
hs-CRP	High sensitivity C-reactive protein
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IP	Investigational product
IM	Intramuscular

Abbreviation	Description
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LS	Least-squares
MDRD	Modification of Diet in Renal Disease formula
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	Nonsteroidal anti-inflammatory drug
PD	Pharmacodynamic
PGA	Physician's global assessment
PK	Pharmacokinetic
PP	Per protocol
PRN	As needed
PT	Preferred term
QD	Once daily
QOD	Once every other day
RBC	Red blood cells
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SLE	Systemic lupus erythematosus
SLEDAI	Systemic lupus erythematosus Disease Activity Index
SLICC	Systemic Lupus International Collaborating Clinics
SOC	System organ class
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States

Abbreviation	Description
VA	Visual acuity
WBC	White blood cells
WHODD	World Health Organization Drug Dictionary

2. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations for Celgene's protocol 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 (SLE)." This SAP pertains to Part 1 of the study design only. Analysis of Part 2 of the study design will be presented in a separate document. This SAP contains definitions of analysis populations, derived variables, and statistical methods for the analysis of efficacy, safety, pharmacokinetic (PK), and pharmacodynamic (PD) parameters.

The analyses in this SAP include:

1. Safety and efficacy analyses based on a database cut after eight subjects from each dose group have completed 28 days of treatment or have discontinued early (referred to as the Day 28 database hereafter);
2. CCI safety, PK, CCI analyses based on a database cut after all subjects have completed Day 85/Visit 10 with 12 weeks of observational follow-up or have discontinued early (referred to as the Day 169 database hereafter).

This SAP provides a more technical and detailed elaboration of the statistical analyses, as outlined and/or specified in the CC-220-SLE-001 study protocol dated 05Jan2016. The SAP will be finalized and approved prior to the unblinding of the final Part 1 database. All statistical analyses detailed in this SAP will be conducted using SAS® Version 9.2 or higher.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective is for Part 1 study

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

3.2. Secondary Objectives

The secondary objective of the study is for Part 1 study

- To describe the PK of CC-220 for subjects with SLE

CCI [redacted]

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

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 three parts, below is the study design for 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 protocol 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 PRN, 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 protocol 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 protocol 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.

Subjects who participate in Part 1 of the study will not be permitted to participate in Part 2 of the study.

4.2. Study Endpoints

Safety, CCI PK, CCI endpoints are listed in Sections 4.2.1 through 4.2.3.

4.2.1. Primary Endpoint

The primary endpoints will assess safety and tolerability.

The following safety parameters will be evaluated throughout the duration of the study:

- Adverse events
  - Type, frequency, severity and relationship of AEs to IP
  - Number of subjects who discontinue IP due to any AE
- Laboratory evaluations for hematology, serum chemistry, and urinalysis will be collected.
  - Laboratory parameters for hematology will include: red blood cells (RBC), hemoglobin (HgB), hematocrit, white blood cells (WBC) and differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils [percent and absolute]), and platelet count.
  - Laboratory parameters for serum chemistry will include: total protein, albumin, calcium, phosphorus, glucose, uric acid, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST; serum glutamic-oxaloacetic transaminase [SGOT]), alanine aminotransferase (ALT; serum glutamic pyruvic transaminase [SGPT]), lipase, sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, lactate dehydrogenase (LDH), and magnesium. Additionally, The central lab will calculate and report the estimated glomerular filtration rate (eGFR) in mL/min using the Modification of Diet in Renal Disease formula (MDRD eGFR).
  - Laboratory parameters for urinalysis dipstick include: microscopic and quantitative protein.
  - Laboratory parameters for micronutrients include: apolipoproteins, total cholesterol, and lipid-soluble vitamins A,D,E,K)
  - Laboratory parameters for inflammation panel include: high sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), fibrinogen, and serum amyloid A.
  - Laboratory parameters for assessment of immunoglobulins include: immunoglobulin G (IgG), immunoglobulin M (IgM), and immunoglobulin A (IgA).
  - Laboratory parameters for assessment of blood clotting include: prothrombin time, internationalized normalized ratio, and partial thromboplastin time.
- Laboratory endpoints include:
  - Number and percentage of subjects with marked abnormalities (see Section 18.3)
  - Observed value and change from Baseline over time

  - Shift from Baseline to postbaseline time points and to the worst postbaseline value in terms of normal/abnormal (low or high) in hematology and serum chemistry laboratory parameters

- Vital signs and weight endpoints include:
  - Change from Baseline over time in vital sign parameters (temperature, pulse, weight and seated blood pressure)
  - Shift from Baseline to postbaseline time-points and to worst postbaseline value in terms of normal/abnormal (see Section 11.3) in blood pressure and pulse
- Electrocardiogram (ECG, 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. The ECG endpoints include:
  - Change from Baseline over time in ECG parameters
  - Number and percentage of subjects with clinically significant electrocardiogram findings
  - Shift from Baseline to postbaseline time points and to worst postbaseline value in terms of normal/abnormal in ECG findings
- Physical examination will include skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal system evaluations. Results of the physical examinations will be recorded only in the source documents, however clinically significant changes in physical examination findings will be captured as AEs.
- Ophthalmological examinations will include visual acuity (VA) and slit lamp exams with fluorescein staining following papillary dilation. Ophthalmological endpoints include:
  - Number and percentage of subjects with clinically significant ophthalmological findings
- Change from Baseline in tetanus toxoid titer at Day 85/Early Termination and Day 113

4.2.2. Secondary Endpoints

The secondary endpoints will assess the PK of CC-220 in plasma. CCI [redacted]

4.2.2.1. Pharmacokinetic Parameters

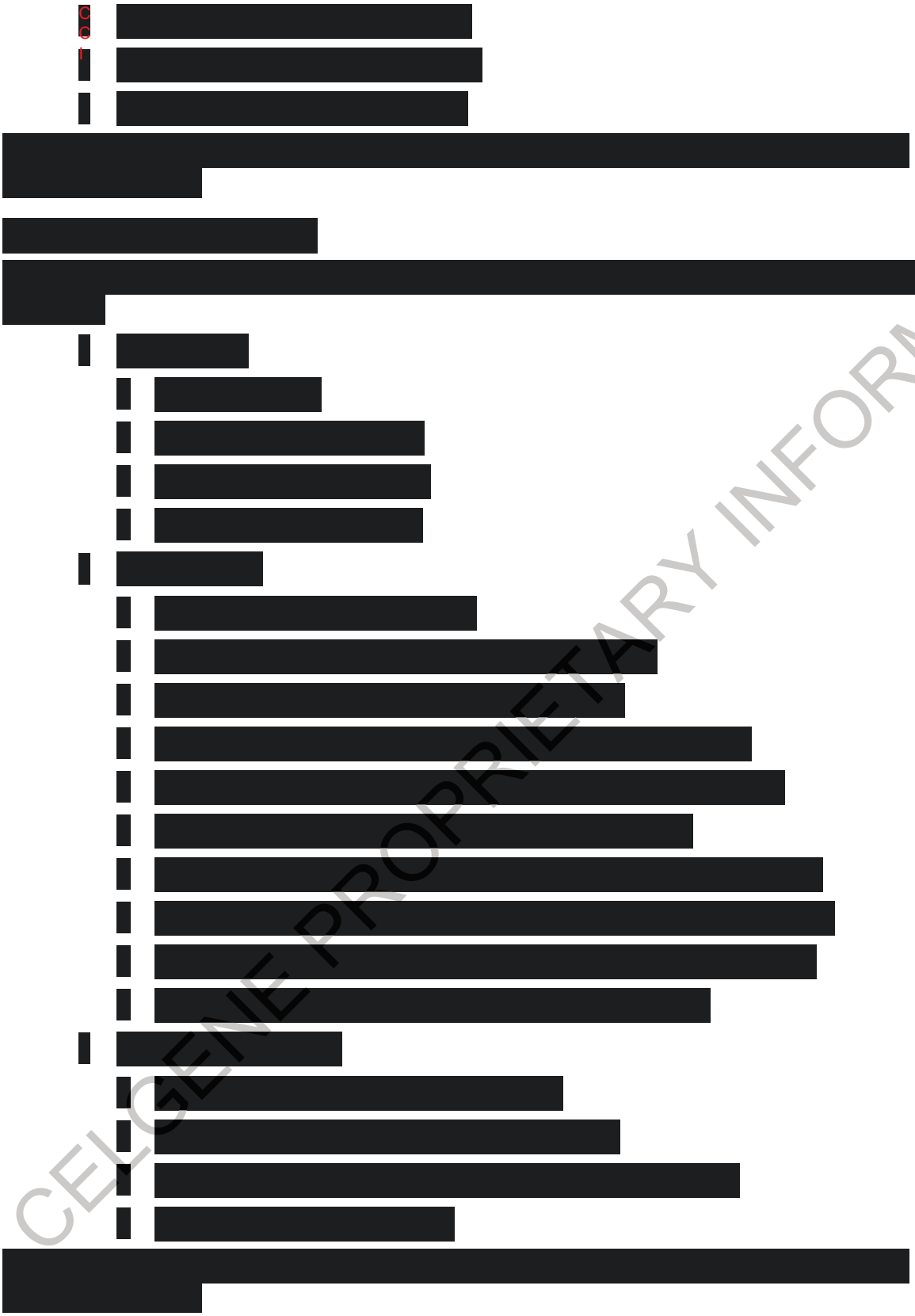
The plasma concentration-time data will be used to determine the PK parameters at Day 1 and Day 29. Standard noncompartmental analysis methods (Phoenix WinNonLin 6.3) will be utilized to obtain the PK parameters presented in Table 2.

Table 2: Plasma Pharmacokinetic Parameters

Parameter	Description
AUC_t	Area under the plasma-concentration time curve from time zero to the last measurable concentration
AUC_τ	Area under the plasma-concentration time curve over one dosing interval from time zero to τ
AUC_{inf}	Area under the plasma-concentration time curve from time zero to infinity
C_{max}	Peak plasma concentration
C_{trough}	Trough plasma concentration
t_{max}	Time to reach peak plasma concentration
$t_{1/2}$	Half-life
CL/F	Apparent oral clearance
Vz/F	Apparent volume of distribution

CCI [redacted]

- CCI [redacted]



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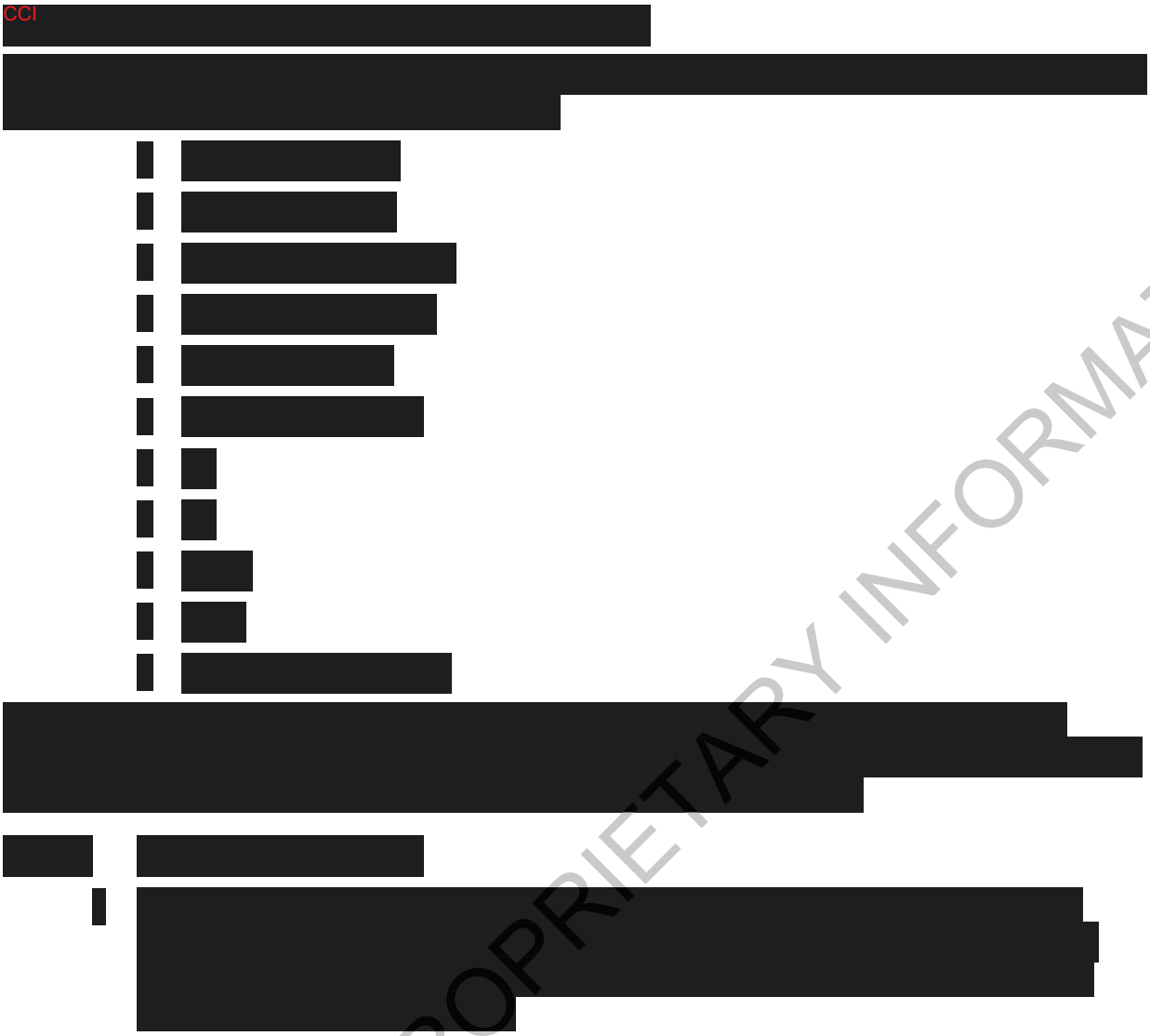

4.3. Stratification, Randomization, and Blinding

Approximately 40 subjects 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 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). 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 alternating QD dose group followed by the 0.6 mg QD dose group).

Randomization Scheme;

Dose group 1 and Dose group 2:

1. Dose groups 1 and 2 will be enrolled at the same time. The subjects are randomized into either Dose group 1 or Dose group 2, stratified by Intensive PK or Non-Intensive PK. When the

number of Non-Intensive PK subjects reaches approximately 8 per dose group, only Intensive PK subjects will be enrolled.

2. Then, the subjects will be randomized to CC-220 or placebo with a 4:1 ratio.

Dose group 3 and Dose group 4:

1. After the interim analysis of Dose group 1 and Dose group 2, Dose group 3 will be enrolled. The subjects will be randomized to CC-220 or placebo with a 4:1 ratio. If the number of Non-Intensive PK subjects reaches approximately 8, only Intensive PK subjects will be enrolled. After the interim analysis of Dose group 3, Dose group 4 will be randomized in the same manner as Dose group 3.

Treatment assignments will be blinded throughout the study. After all Part 1 subjects have completed Day 85/Visit 10 with 12 weeks of observational follow-up or have discontinued early, and the database has been locked, treatment will be unblinded.

All randomization schedules will be generated and implemented by an external vendor of the study IVRS/IWRS.

Following completion of the first 28 days of the Treatment Phase by 8 subjects from each dose group, assessments of safety and tolerability will be conducted. Tables, listings, and graphs for disposition, exposure, demographics, efficacy measures, TEAEs, laboratory values, and vital signs will be summarized. The treatment will be kept blinded and tabulations will be presented as a single aggregate group. The first interim analysis will occur with Dose groups 1 and 2 combined since these two dose groups are enrolled simultaneously.

Additional interim analyses, if applicable, (see Section 15) may be performed by an independent team who is not involved in the conduct and data management of the study.

4.4. Sample Size Determination

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

For Part 1, a total of approximately 40 subjects will be randomized to 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.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Reporting Conventions

Summary statistics for continuous variables include sample size (n), mean, standard deviation (SD), median, minimum, and maximum. All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented to the same number of decimal places as the measured value. The frequency summary for categorical variables includes number and percentage. All percentages will be rounded to one decimal place. Number and percentage values will be presented as xx (xx.x). All analysis and summary tables will have the population sample size for each treatment group in the column heading. Any p-values (2-sided) will be presented with four decimal places. All laboratory data will be reported using standard international units.

In data derivations requiring the date of the first dose of IP dispensed at a specific visit, in the absence of a definitive record of this date, the study drug dispense date (from the study drug accountability records) associated with that visit, or if this date is also missing, then the visit date, will be used to estimate the date of the first dose of IP in question. In the absence of a definitive record of the date of the last dose of IP for subjects who have completed the study or have discontinued early, the date of the Day 85/Visit 10 visit or the discontinuation visit will be used to estimate the last dose date for subjects who have completed the study or have discontinued early and have the discontinuation visit; for subjects who have discontinued but do not have the discontinuation visit, the last "follow-up" date (ie, the maximum date among the subject's records of study visits, study drug records, AEs [start and end dates], concomitant medications/procedures, laboratory, vital signs, and ECG) will be used to estimate the last dose date.

In the event of dose interruption or reduction (see Section 4.1), the subject will be included in the treatment group to which they were originally assigned.

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

5.2. Baseline Definition

The baseline is defined as the last value measured on or before the day of the first dose of IP.

5.3. Time Points

Time points (including the scheduled study days per protocol, the end of treatment, and the observational follow-up visit) in all analyses are based on the visits/study days as recorded in the database.

Appropriate dates (eg, date of measurement or date of specimen collection) will first be used to ensure only data (including data from scheduled, unscheduled, discontinuation, and observational follow-up visits) measured or collected within the specific analysis period are

included, and then the visits/study days as recorded in the database will be used to assign one value (possibly missing) to each time point at the subject level according to the following rules:

- If a value is available at a scheduled visit (eg, Day 15/Visit 4), then that value will be used for the study day, regardless of whether a value is available from an unscheduled visit (eg, Visit 4.01) that is associated with the scheduled visit.
- If the value at a scheduled visit is missing but a value is available at an associated unscheduled visit, the value from the associated unscheduled visit will be used for the study day. If values from more than one associated unscheduled visit (eg, Visits 4.01 and 4.02) are available, then the one from the first associated unscheduled visit (eg, Visit 4.01) will be used for the study day.
- If the value at a scheduled visit is missing and there is no value available from an associated unscheduled visit, the value at the study day will be missing.
- A value from the discontinuation visit (for a discontinued subject) will be mapped to the next scheduled visit after the last visit the subject has completed.
- The end of treatment is defined as the last postbaseline visit among all the scheduled and unscheduled visits and, if applicable, the discontinuation visit; the observational follow-up visit is not included in the derivation of the end of treatment value.

5.4. Analysis Populations

5.4.1. Intent-to-Treat Analysis Set

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

5.4.2. Per Protocol Analysis Set

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

5.4.3. Safety Population

The Safety Population will include all subjects who are randomized and receive at least one dose of IP. The safety analyses will be based on the Safety Population. Subjects will be included in the treatment group corresponding to the IP they actually received for the safety analyses. For most subjects, this will be the treatment group to which they are randomized. For 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. If a subject undergoes a dose reduction (see protocol section 8.2) the subject will be included in the treatment group corresponding to the initial IP that they receive.

CCI [redacted]

[redacted]

5.4.5. Pharmacokinetic Population

The PK population will include all subjects in the safety population with at least one non-missing plasma concentration data. The PK Population will be the population used for the PK analyses. Subjects will be included in the treatment group to which they are randomized for the PK analyses.

6. SUBJECT DISPOSITION

The number of subjects screened, the number and percentage of subjects randomized (as recorded in the IVRS database), the number and percentage of subjects not randomized among all subjects screened, and the eligibility criteria failed will be summarized. The failed inclusion/exclusion criteria of subjects who were screened and not randomized will be included in the summary. The above percentages will be based on the number of subjects screened.

The number and percentage of subjects included in each analysis population will be summarized by treatment group. The percentages will be based on the number of subjects randomized. A listing of subjects excluded from the analysis populations, with the reasons for exclusions, will be provided.

The number and percentage of subjects who entered, completed, and discontinued each study phase (Treatment Phase and Observational Follow-up Phase), and the number and percentage of primary reasons for discontinuation for subjects who early discontinued will be summarized. The percentages will be based on the number of subjects randomized.

The primary reason for discontinuation is collected in the study disposition electronic case report form (eCRF) and will be summarized with the following categories:

- Screen Failure
- Death
- Adverse event
- Withdrawal by subject
- Lost to follow-up
- Protocol violation
- Other

Listings will be provided for subjects randomized but not treated, and for discontinued subjects with reason for treatment discontinuation.

7. PROTOCOL DEVIATIONS/VIOLATIONS

The protocol deviations/violations will be identified and assessed by the study team in accordance with Celgene's standard operating procedure. The protocol deviations/violations for a particular analysis will be defined prior to unblinding of the database. The protocol deviations/violations will be summarized by treatment group for the ITT analysis set. A by-subject listing of subjects with protocol deviations/violations will be provided.

8. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The demographics and baseline characteristics will be summarized descriptively by treatment group for the ITT analysis set. Individual subject listings will be provided to support the summary tables.

8.1. Demographics

Demographic variables include:

- Age (years)
- Age category (< 40, 40 to < 65, ≥ 65 years)
- Sex (male, female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Weight (kg)
- Weight category (< 70, ≥ 70 to < 85, ≥ 85 to < 100, ≥ 100 kg)
- Height (cm) at Screening
- Body mass index (BMI; kg/m^2)
- BMI category (< 25, ≥ 25 to < 30, ≥ 30 to < 35, ≥ 35 to < 40, ≥ 40 kg/m^2)
- Alcohol use (never, current, former user)
- Tobacco use (never, current, former user)
- Caffeine use (never, current, former user)

8.2. Baseline Characteristics

Baseline characteristics include:

- Duration of SLE (years)
- [redacted]

[redacted]

8.3. Medical History

Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA; Version 17.0 or higher). A frequency summary of medical history will be presented by treatment group, system organ class (SOC), and preferred term (PT) for the ITT analysis set. A data listing including the verbatim and coded terms will be presented.

A frequency summary of SLE medical history will also be presented by treatment group for the ITT analysis set.

8.4. Prior and Concomitant Medications

Medications that were initiated prior to the start of study treatment and which continued after the start of study treatment will be counted as both prior and concomitant medications. The Anatomical Therapeutical Chemical (ATC) coding scheme of the World Health Organization Drug Dictionary (WHODD; Version March 2014 or higher) will be used to group medications into relevant categories. A data listing including the verbatim and coded terms will be presented.

8.4.1. Prior Medications

Prior medications are defined as medications that were started before the start of study treatment and either ended before the start of study treatment or continued after study treatment. A frequency summary of prior medications will be provided by treatment group, ATC1 level, and standardized medication name for the ITT analysis set.

8.4.2. Concomitant Medications

Concomitant medications are defined as medications that were initiated before the first dose of IP and continued during the study treatment, or initiated on/after the date of the first dose of IP and on/before the date of treatment discontinuation. A frequency summary of concomitant medications will be provided by treatment group, ATC1 level and standardized medication name for the Safety Population.

8.5. Prior and Concomitant Procedures

Procedures will be coded according to MedDRA, Version 17.0 or higher.

8.5.1. Prior Procedures

Prior procedures are defined as procedures or surgeries that occurred before the first dose of IP. A frequency summary of prior procedures will be presented by treatment group, SOC, and PT for the ITT analysis set.

8.5.2. Concomitant Procedures

Concomitant procedures will be identified similar to the criteria in Section 8.4.2. A frequency summary of concomitant procedures will be provided by treatment group, SOC, and PT for the Safety Population.

9. STUDY TREATMENTS AND EXTENT OF EXPOSURE

9.1. Treatment Duration

Treatment duration (in weeks) is calculated as (the date of the last dose of IP – the date of the first dose of IP + 1) / 7 and rounded to one decimal place.

Treatment duration will be summarized by treatment group for the Safety Population. Frequency summaries of treatment duration will also be presented for the following categories: < 1, ≥ 1 to < 2, ≥ 2 to < 4, ≥ 4 to < 8, ≥ 8 to < 12, and ≥ 12 weeks.

A subject data listing of study drug records will be provided.

9.2. Treatment Compliance

As part of the routine recording of the amount of IP taken by each subject, the number of tablets dispensed and returned will be recorded at each visit after Visit 1. These records will be used to calculate treatment compliance. A subject data listing of drug accountability records will be provided.

The compliance rate (%) for each subject for a period will be computed as 100 times the total number of tablets taken (the total number of tablets dispensed minus the total number of tablets returned) over the period divided by the intended total number of tablets that should have been taken over the same period.

The intended total number of tablets is calculated as follows. First chronologically order the first dose date, the second dispense date, the third dispense date, etc., up to the last dose date. The first and last dose dates are defined in the same way as those defined for treatment duration calculations (see Section 9.1). The intended number of tablets between any two consecutive dates is calculated as $2 \times n$, where n denotes the number of days between the 2 consecutive dates (ie, the second date minus the first date for all pairs of consecutive dates, and the second date minus the first date plus 1 for the last pair). Then the intended total number of tablets is the sum of all intended numbers of tablets as calculated above from the first dose date through the last dose date. Of note, compliance rate will not be calculated for subjects (if existent) who have only the dispense record at Day 1/Visit 2 and no other drug accountability records.

Treatment compliance will be summarized by treatment group for the Safety Population. Frequency summaries of compliance rate will also be presented with the following categories: < 75%, ≥ 75% to ≤ 120%, and > 120%.

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11. SAFETY ANALYSIS

The purpose of this section is to define the safety parameters for the study. All summaries of safety data will be performed for the Safety Population.

For the analyses of TEAEs and marked abnormalities, subject incidence will be provided, unless otherwise specified. Subject incidence (ie, percentage [%] used in a frequency summary) is defined as 100 times the number of subjects with the specific event divided by the number of subjects included in the analysis. Subjects with multiple occurrences of the specific event in the specific analysis period will be counted only once in the numerator.

Summaries of safety parameters over time (eg, summary statistics over time and shifts from Baseline to postbaseline time points in terms of normal/abnormal) will include data collected at scheduled, unscheduled, and discontinuation visits up to 28 days after the last dose of study drug in the study and data collected at observational follow-up visits. Summaries of marked abnormalities and shifts from Baseline to worst postbaseline value will include all data up to 28 days after the last dose of study drug in the study, irrespective of the visits from which these data are collected. The "worst" lab results will be defined using the worst of all post-baseline reference range indicators and grouped into "LOW" or "HIGH" or "Both L and H" or "NORMAL".

In summaries of continuous variables with summary statistics by time point, values for Baseline, time point, and change from Baseline will be summarized at each time point for subjects who have both values at Baseline and at the time point. Similarly, in frequency summaries of shifts from Baseline, only subjects who have both values at Baseline and at the time point will be included in the summaries of shifts to the scheduled study days per protocol and only subjects who have a Baseline value and at least one postbaseline value will be included in the summaries of shifts to the end of period and to the worst postbaseline value.

11.1. Adverse Events

Adverse events will be analyzed in terms of treatment-emergent adverse events (TEAE) which are defined as any AEs that begin or worsen on or after the start of study drug through 28 days after the last dose of study drug or study treatment discontinuation date, whichever is later. All AEs will be coded using MedDRA Version 17.0 or higher. A subject data listing of all AEs, including the verbatim and coded terms, will be presented.

Unless otherwise specified, AEs will be summarized by SOC and PT, with SOCs presented in the standard international order and PTs within each SOC in descending order of subject incidence (and then alphabetically if needed).

An overall summary of the following AE categories will be provided:

- Any TEAE
- Any drug-related TEAE
- Any severe TEAE
- Any serious TEAE

- Any serious drug-related TEAE
- Any TEAE leading to drug interruption
- Any TEAE leading to drug withdrawal
- Any TEAE leading to death

Specific TEAEs under each of the above categories will be summarized.

A drug-related TEAE is defined as a TEAE which is considered to be of suspected relationship to study drug. Adverse events with missing relationship to study drug will be assessed as drug-related.

If a subject reports multiple occurrences of a specific event within a specific analysis period, the subject will be counted only once by the maximum severity (mild, moderate, severe, and, if needed, missing). If the severity is missing for one or more of the occurrences, the maximum severity of the remaining occurrences will be used. If the severity is missing for all of the occurrences, the subject will be counted only once in the "missing" category of severity.

11.1.1. All Treatment-emergent Adverse Events

All TEAEs will be summarized by SOC and PT as well as by PT only (in descending order of subject incidence).

All TEAEs will be summarized by age category (< 40, ≥ 40 years) and sex (Male, Female).

All TEAEs occurring after the date of the last dose of IP and up to 28 days after the last dose of IP will also be summarized by SOC and PT for subjects who enter the observational follow-up phase.

11.1.2. Drug-related Treatment-emergent Adverse Events

Drug-related TEAEs will be summarized.

11.1.3. Treatment-emergent Adverse Events by Maximum Severity

All TEAEs will be summarized by maximum severity (mild, moderate, severe, and, if needed, missing). If a subject reports multiple occurrences of a specific event within a specific analysis period, the subject will be counted only once by the maximum severity. If the severity is missing for one or more of the occurrences, the maximum severity of the remaining occurrences will be used. If the severity is missing for all of the occurrences, the subject will be counted only once in the "missing" category of severity.

11.1.4. Serious Treatment-emergent Adverse Events

Serious TEAEs will be summarized by SOC and PT as well as by PT only (in descending order of subject incidence).

Serious drug-related TEAEs will be summarized.

A subject data listing of all serious AEs (both TEAEs and non-TEAEs) will be provided.

11.1.5. Treatment-emergent Adverse Events Leading to Drug Interruption and Leading to Drug Withdrawal

Treatment-emergent AEs leading to drug interruption will be summarized.

Treatment-emergent AEs leading to drug withdrawal will also be summarized. A subject data listing of TEAEs leading to drug withdrawal will be provided.

11.1.6. Treatment-emergent Adverse Events Leading to Deaths

Treatment-emergent AEs leading to death will be summarized. A subject data listing of all deaths will be provided.

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11.2. Clinical Laboratory Evaluations

Summary statistics of observed values and changes from Baseline in hematology and serum chemistry laboratory parameters will be provided over time. Frequency summaries (shift tables) of shifts from Baseline to postbaseline time points and to the worst postbaseline value in terms of

normal/abnormal will be provided for hematology and serum chemistry. The urinalysis results will be provided only in a listing.

Laboratory marked abnormalities (see Table 7) will be summarized; subject incidence for each abnormality will be calculated based on subjects with a baseline value and at least one postbaseline value for criteria requiring baseline or subjects with at least one postbaseline value for criteria not requiring baseline. A subject data listing of laboratory marked abnormalities will be provided.

A subject data listing of all laboratory data will be provided.

11.3. Vital Sign Measurements

Summary statistics of observed values and changes from Baseline in vital signs will be provided over time. Frequency summaries (shift tables) of shifts from Baseline to postbaseline time points and to the worst postbaseline value in terms of normal/abnormal will be provided for pulse and blood pressure. The normal ranges are defined as: 60 to 100 beats/minute for pulse, 90 to 140 mm Hg for systolic blood pressure, and 60 to 90 mm Hg for diastolic blood pressure.

A subject data listing of all vital signs and weight data will be provided.

11.4. Electrocardiograms

Summary statistics of observed values and changes from Baseline in ECG findings will be provided over time. For each parameter, triplicate ECG readings will be averaged and this average used as the result in summary statistics. The overall ECG interpretation will be summarized by presenting the number and percentage of subjects with 'Normal', 'Abnormal, not clinically significant', and 'Abnormal, clinically significant' by treatment. The shift from Baseline to worst during the treatment in the overall ECG interpretation will be displayed for each treatment.

11.5. Ophthalmological Examination

The overall interpretation will be summarized by presenting the number and percentage of subjects with 'Normal', 'Abnormal, not clinically significant', and 'Abnormal, clinically significant' by treatment. The shift from Baseline to Day 85/Early Termination in the overall interpretation will be displayed for each treatment.

11.6. Physical Examination

No summary of physical examination findings will be provided. Clinically significant changes in physical examination findings will be captured as AEs.

11.7. Tetanus Toxoid

Summary statistics of observed values and change from Baseline will be provided over time.

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13. PHARMACOKINETIC ANALYSIS

All PK analyses will be conducted using the PK Population.

Plasma concentration data will be presented in descriptive summary tables, individual listings, mean profile plots, and individual profile plots. Descriptive statistics for plasma concentrations will include n, arithmetic mean, SD, coefficient of variation (CV%), median, minimum, maximum, geometric mean and geometric CV% (GeoCV%). Plasma concentrations below the quantifiable limit will be treated as zero (0) for the computation of arithmetic mean and a concentration value of 50% of the low limit of quantification for the computation of geometric mean.

Descriptive statistics for PK parameters will include n, arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean and GeoCV%.

CV% will be calculated as 100*(SD/arithmetic mean).

GeoCV% will be calculated as 100*sqrt[exp(SDlog^2)-1], where SDlog is the SD of the natural log transformed values.

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15. INTERIM ANALYSIS

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. Data for disposition, exposure, demographics, CCI [redacted], TEAE, laboratory values, and vital signs will be reviewed. The treatment will be kept blinded.

Results will be used to assess safety and to determine if the next dose group will be enrolled.

After all Part 1 subjects have completed Day 85/Visit 10 with 12 weeks of observational follow-up or have discontinued early, and the database has been locked, treatment will be unblinded.

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16. CHANGES TO THE STATISTICAL ANALYSES SECTION OF THE PROTOCOL

No changes to the statistical analyses section of the protocol are made in this SAP.

17. REFERENCES

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18. APPENDICES

18.1. Handling of Dates

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (ie, the Date9. datetime format in SAS). Dates in the clinical database are classified into the categories of procedure dates, log dates, milestone dates, outcome dates, and special dates.

- **Procedure Dates** are the dates on which given protocol-specified procedure are performed. They include the dates of laboratory testing, physical examinations, tumor scans, etc. They should be present whenever data for a protocol-specified procedure are present and should only be missing when a procedure is marked as NOT DONE in the database. Procedure dates will not be imputed.
- **Log Dates** are dates recorded in CRF data logs. Specifically, they are the start and end dates for AEs and concomitant medications/procedures. They should not be missing unless an event or medication is marked as *ongoing* in the database. Otherwise, incomplete log dates will be imputed according to the rules in Appendix 18.2 (eg, for duration or cycle assignment, etc). However, in listings, log dates will be shown as recorded without imputation.
- **Milestone Dates** are dates of protocol milestones such as randomization, study drug start date, study drug termination date, study closure date, etc. They should not be missing if the milestone occurs for a subject. They will not be imputed.
- **Special Dates** cannot be classified in any of the above categories and they include the date of birth. They may be subject to variable-specific censoring and imputation rules.

Dates recorded in comment fields will not be imputed or reported in any specific format.

18.1.1. Calculations Using Dates

Calculations using dates (eg, subject's age or relative day after the first dose of study drug) will adhere to the following conventions:

18.1.1.1. Study Day

Study days after the start day of study drug (first dose date) will be calculated as follows:

- **For dates of interest on or after the first dose date:** The study days will be calculated as the difference between the date of interest and the first dose date of study medication plus 1 day.
  STUDY DAY= (TARGET DATE – DSTART) + 1;
  where DSTART = the first dose date.
- **For dates of interest prior to the first dose date:** The study days will be calculated as the difference between the date of interest and the first dose date of study medication only.

STUDY DAY= TARGET DATE – DSTART;
where DSTART = the first dose date.

- Study Day 1 is the first day of treatment of study drug. Negative study days are reflective of observations obtained during the baseline/screening period.
- Partial dates for the first study drug are not imputed in general. All effort should be made to avoid incomplete study drug start dates. Some analyses may exclude subjects without study drug start date. The SAP may be amended on a case-by-case basis, including guideline and suggestion such as imputing Day 1 by consent date of treated patient.

18.1.1.2. Age

Age (expressed in years) is calculated as the difference between the date of birth and the informed consent date plus 1 day. Age will be transformed to years by dividing the difference by 365.25 days, then truncating.

AGE = Integer portion of (DATE of CONSENT – DATE of BIRTH + 1) /365.25

- Preference is for using calculated age from clinical database. When not available, calculated age from CRF or IVRS may be used
- Partial birth date: impute missing day as 15th of the month; impute missing month as July; set missing age for missing year
- Intervals that are presented in weeks will be transformed from days to weeks by using (without truncation) the following conversion formula:
  WEEKS = DAYS /7
- Intervals that are presented in months will be transformed from days to months by using (without truncation) the following conversion formula:
  MONTHS = DAYS /30.4167

18.1.1.3. Duration of Systemic Lupus Erythema

Duration of SLE (expressed in years) is calculated as the difference between the date of diagnosis of SLE and the informed consent date plus 1 day divided by 365.25 days, then rounded to 1 decimal.

Duration of SLE = (DATE of CONSENT – DATE of SLE DIAGNOSIS + 1) /365.25

Partially missing SLE diagnosis dates will be imputed as specified in Section 18.2.3.

18.2. Date Imputation Guideline

18.2.1. Adverse Events

Partially missing AE start dates will be imputed in the analysis dataset model (ADaM) dataset for AEs, but partially missing AE end dates will not be imputed in the same dataset. If the AE end date is complete with no missing year, month, or day, and the partially missing start date imputed by the rules below is after the AE end date, then the start date will be imputed by the AE end date.

The principle of the imputation rules is to treat the AE as treatment-emergent, ie, occurring on or after the date of the first dose of IP, if possible.

Let an AE start date be represented as "$D_{Event}/M_{Event}/Y_{Event}$", and the date of the first dose of IP as "$D_{IP}/M_{IP}/Y_{IP}$". The imputation rules for partially missing AE start dates are stated in Table 3.

Table 3: Imputation Rules for Partially Missing Adverse Event Start Date

Scenario	Condition	Imputation Rule
A. Partially missing date includes year only (both month and day are missing)		
1	$Y_{Event} < Y_{IP}$	$31/12/Y_{Event}$
2	Otherwise, ie, $Y_{IP} \leq Y_{Event}$	Max (date of first dose of IP, $01/01/Y_{Event}$)
B. Partially missing date includes both year and month (only day is missing)		
1	$Y_{Event} < Y_{IP}$, or ($Y_{Event} = Y_{IP}$ and $M_{Event} < M_{IP}$)	Last date of M_{Event}/Y_{Event}
2	Otherwise, ie, $Y_{IP} < Y_{Event}$, or ($Y_{IP} = Y_{Event}$ and $M_{IP} \leq M_{Event}$)	Max (date of first dose of IP, $01/M_{Event}/Y_{Event}$)

18.2.2. Prior/Concomitant Medications/Procedures

Partially missing start/stop dates for prior/concomitant medications and partially missing start dates for prior/concomitant procedures will be imputed in the ADaM dataset. For prior/concomitant medications, if the stop date is complete with no missing year, month, or day, and the partially missing start date imputed by the rule below is after the stop date, then the start date will be imputed by the stop date.

Partially missing prior/concomitant medication/procedure start dates will be imputed by the earliest possible date given the non-missing field(s) of the date.

Partially missing prior/concomitant medication stop dates will be imputed by the latest possible date given the non-missing field(s) of the date.

Let a prior/concomitant medication/procedure start/stop date be represented as "$D_{Event}/M_{Event}/Y_{Event}$". The imputation rules for partially missing prior/concomitant medication start dates are stated in Table 4. The imputation rules for partially missing prior/concomitant medication stop dates are stated in Table 5.

Table 4: Imputation Rules for Partially Missing Prior/Concomitant Medication/Procedure Start Dates

Scenario	Condition	Imputation Rule
1	Partially missing date includes year only (both month and day are missing)	$01/01/Y_{Event}$
2	Partially missing date includes both year and month (only day is missing)	$01/M_{Event}/Y_{Event}$

Table 5: Imputation Rules for Partially Missing Prior/Concomitant Medication Stop Dates

Scenario	Condition	Imputation Rule
1	Partially missing date includes year only (both month and day are missing)	$31/12/Y_{Event}$
2	Partially missing date includes both year and month (only day is missing)	Last date of M_{Event}/Y_{Event}

18.2.3. Medical History

Partially missing medical history start dates will be imputed in the ADaM dataset for medical history (for the purposes of calculating duration of SLE). The 16th of the month will be used to impute a partially missing start date that has only the day missing, and July 1st will be used to impute a partially missing start date that has both the month and day missing.

Let a medical history start date be represented as "$D_{Event}/M_{Event}/Y_{Event}$". The imputation rules for partially missing medical history start dates are stated in Table 6 .

Table 6: Imputation Rules for Partially Missing Medical History Start Dates

Scenario	Condition	Imputation Rule
1	Partially missing date includes year only (both month and day are missing)	$01/07/Y_{Event}$
2	Partially missing date includes both year and month (only day is missing)	$16/M_{Event}/Y_{Event}$

18.3. Marked Abnormalities Criteria

The laboratory marked abnormality criteria is presented in Table 7.

Table 7: Laboratory Marked Abnormality Criteria

Category / Analyte	SI Units	Criteria
Chemistry		
Alanine Aminotransferase (SGPT)	U/L	> 3 xULN
Albumin	Kg/m^3	< 25
Alkaline Phosphatase	U/L	> 400
Aspartate Aminotransferase (SGOT)	U/L	> 3 x ULN
Total Bilirubin	µmol/L	> 1.8 x ULN
Blood Urea Nitrogen	mmol/L	> 15
Calcium	mmol/L	< 1.8 > 3.0
Creatinine	µmol/L	> 1.7 x ULN
Glucose	mmol/L	< 2.8 > 13.9
Hemoglobin A1C	%	> 9

Category / Analyte	SI Units	Criteria
Lactate Dehydrogenase	U/L	> 3 x ULN
Magnesium	mmol/L	> 1.2
Phosphate	mmol/L	< 0.64 > 1.60
Potassium	mmol/L	< 3.0 > 5.5
Sodium	mmol/L	< 130 > 150
Triglycerides	mmol/L	> 3.4
Urate	umol/L	Male: > 590; Female: > 480
Alanine Aminotransferase (SGPT) Aspartate Aminotransferase (SGOT) Total Bilirubin	U/L U/L µmol/L	(ALT > 3xULN or AST > 3xULN) and Total Bilirubin > 1.5x ULN
Hematology		
Hemoglobin	g/L	Male: < 10.5, Female: < 8.5 Male: > 18.5, Female: > 17
Leukocytes	10^9/L	< 1.5
Lymphocytes	10^9/L	< 0.8
Neutrophils	10^9/L	< 1.0
Platelets	10^9/L	< 75 > 600

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