

STATISTICAL ANALYSIS PLAN

Final Version 1.0

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**Rituximab Plus Cyclophosphamide Followed by Belimumab  
for the Treatment of Lupus Nephritis**

PROTOCOL NUMBER ITN055AI

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## 1. PROTOCOL SYNOPSIS

<b>Title</b>	Rituximab Plus Cyclophosphamide followed by Belimumab for the Treatment of Lupus Nephritis
<b>Short Title</b>	Rituximab and Belimumab for Lupus Nephritis
<b>Sponsor</b>	NIAID
<b>Conducted By</b>	Immune Tolerance Network
<b>Protocol Chairs</b>	Betty Diamond, MD; David Wofsy, MD; Cynthia Aranow, MD; Maria Dall'Era MD
<b>Accrual Objective</b>	40 participants
<b>Study Treatment</b>	Study treatment will be rituximab, cyclophosphamide (CTX), and Solumedrol. This treatment will be followed by prednisone and belimumab in one group, and by prednisone without belimumab in the other group.
<b>Study Design</b>	<p>This trial will be conducted as a prospective randomized phase 2 open label multicenter study in individuals with active lupus nephritis age 18 and older. There will be two treatment arms with 1:1 randomization of a total of 40 participants.</p> <p>During the treatment phase, all participants will receive infusions of Solumedrol 100mg, rituximab 1000mg, and CTX 750mg intravenously (IV) at week 0 and week 2. Prednisone 40 mg per day will be administered with a guided steroid taper to 10mg per day by week 12. Participants will be randomized at week 4 to either the Rituximab/Cyclophosphamide (RC) Group or the Rituximab/Cyclophosphamide/Belimumab (RCB) Group. The RC Group will be maintained on prednisone. The RCB Group will receive IV belimumab 10mg/kg at weeks 4, 6, 8, and then every 4 weeks through week 48 in addition to prednisone. During the tolerance assessment phase, intravenous study medication will be discontinued after week 48, and all participants will be maintained on prednisone through week 96 of the study.</p>
<b>Study Duration</b>	Total study duration will be 200 weeks. The enrollment period for this study will be 104 weeks. Study participation period will be 96 weeks, which includes a treatment phase of 48 weeks and a tolerance assessment phase of 48 weeks.
<b>Primary Objective</b>	The primary objective of the study is to assess the safety of belimumab administration following treatment with rituximab and CTX, in terms of infectious adverse events.
<b>Primary Endpoint</b>	The primary endpoint is the proportion of participants who experience at least one Grade 3 or higher infectious adverse event at or prior to week 48.

**Secondary  
Endpoints**

1. Proportion of participants who experience at least one Grade 3 or higher infectious adverse event at or prior to week 24, and at or prior to week 96.
2. Proportion of participants with B cell reconstitution at week 24, 48, and 96, defined as the participant's baseline B cell count, or the lower limit of normal, whichever is lower.
3. Proportion of participants with Grade 4 hypogammaglobulinemia at or before week 24, 48, and 96.
4. Proportion of participants with a complete response at week 24. Complete response is defined as meeting all of the following criteria:
  - Urine protein-to-creatinine ratio (UPCR)  $< 0.5$ , based on a 24-hour collection.
  - Estimated glomerular filtration rate (eGFR)  $\geq 120$  ml/min/1.73m<sup>2</sup> calculated by the CKD-EPI formula or, if  $< 120$  ml/min/1.73m<sup>2</sup>, then  $> 80\%$  of eGFR at entry.
  - Prednisone dose tapered to 10 mg/day, or as specified in section 5.5.2.
5. Proportion of participants with an overall response (complete or partial response) at week 24. A partial response is defined as meeting all of the following criteria:
  - $\geq 50\%$  improvement in the UPCR from study entry, based on a 24-hour collection.
  - Estimated glomerular filtration rate (eGFR)  $\geq 120$  ml/min/1.73m<sup>2</sup> calculated by the CKD-EPI formula or, if  $< 120$  ml/min/1.73m<sup>2</sup>, then  $> 80\%$  of eGFR at entry.
  - Prednisone dose tapered to 10 mg/day, or as specified in section 5.5.2.
6. Proportion of participants with complete response at week 48.
7. Proportion of participants with an overall response (complete or partial response) at week 48.
8. Proportion of participants with complete response at week 96 (cumulative complete response).
9. Proportion of participants with sustained complete response at week 96 (representing "clinical tolerance"). Sustained complete response

is defined as a complete response measured at 48 and 96 weeks.

10. Proportion of participants with an overall response (complete or partial response) at week 96.
11. Proportion of participants with treatment failure at or before week 24, 48, and 96, as defined by withdrawal from the protocol due to worsening nephritis, infection, or study medication toxicity.
12. Frequency of non-renal flares at or before week 24, 48, and 96, defined by the British Isles Lupus Assessment Group (BILAG) criteria.
13. Anti-dsDNA antibodies and C3, C4 levels at week 24, 48, and 96
14. Frequency of the following specific AEs:
  - Any event leading to death.
  - Grade 2 or greater leukopenia or thrombocytopenia.
  - Premature ovarian failure.
  - Malignancy.
  - Venous thromboembolic event (deep venous thrombosis or pulmonary embolism).
  - Disease- or study medication-related event leading to hospitalization.
  - Infusion reactions (within 24 hours of infusion) that result in the cessation of further infusions (including cytokine-release allergic reaction).

**Inclusion Criteria**

1. Diagnosis of Systemic Lupus Erythematosus (SLE) by American College of Rheumatology (ACR) criteria or Systemic Lupus International Collaborating Clinics (SLICC) criteria.
2. Positive antinuclear antibody (ANA) or positive anti-ds DNA test results at visit -1 or any time within 14 days before visit -1.
3. Age 18 years or older.
4. Active proliferative lupus nephritis, as defined by either of the following:
  - a. Kidney biopsy documentation within the last 3 months of ISN/RPS proliferative nephritis: Class III, Class IV, or Class V in combination with Class III or IV.
  - b. Kidney biopsy documentation within the last 18 months of ISN/RPS proliferative nephritis: Class III, Class IV, or Class V



in combination with Class III or IV, associated with at least one of the following:

- i. Active urinary sediment as defined by any one of the following:
    - a.  $>4$  RBC/hpf in the absence of menses and infection;
    - b.  $>5$  WBC/hpf in the absence of infection; or
    - c. cellular casts limited to RBC or WBC casts.
  - ii.  $\text{UPCR} \geq 3$  based on a 24-hour collection at visit -1 or any time within 14 days before visit -1.
  - iii. Confirmed increase in UPCR compared to a prior UPCR determination within 3 months of study entry. An increase in proteinuria will be considered to be confirmed if present on 2 consecutive assessments, or if increase led to a change in treatment. Increase in UPCR is defined as:
    - a.  $\text{UPCR} > 1$  if prior UPCR was  $\leq 0.2$ ;
    - b.  $\text{UPCR} > 2$  if prior UPCR was  $\leq 1$  but  $> 0.2$ ;
    - c.  $\text{UPCR} > \text{double the prior UPCR}$  if prior UPCR was  $> 1$ .
5.  $\text{UPCR} > 1$  based on a 24-hour collection at visit -1 or any time within 14 days before visit -1.
  6. Ability to provide informed consent.

**Exclusion Criteria**

1. New onset lupus nephritis, defined as lupus nephritis for which the participant has not yet been treated with either mycophenolate mofetil or cyclophosphamide.
2. Neutropenia (absolute neutrophil count  $< 1500/\text{mm}^3$ ).
3. Thrombocytopenia (platelets  $< 50,000/\text{mm}^3$ ).
4. Moderately severe anemia (Hgb  $< 8$  mg/dL).
5. Positive QuantiFERON – TB Gold test results. PPD tuberculin test may be substituted for QuantiFERON – TB Gold test.
6. Pulmonary fibrotic changes on chest radiograph consistent with prior healed tuberculosis.
7. Active bacterial, viral, fungal, or opportunistic infections.
8. Evidence of infection with human immunodeficiency virus (HIV),

- hepatitis B (as assessed by HBsAg and anti-HBc) or hepatitis C.
9. Hospitalization for treatment of infections, or parenteral (IV or IM) antibacterials, antivirals, anti-fungals, or anti-parasitic agents within the past 60 days.
  10. Chronic infection that is currently being treated with suppressive antibiotic or antiviral therapy, including but not limited to tuberculosis, pneumocystis, cytomegalovirus, herpes simplex virus, herpes zoster, and atypical mycobacteria.
  11. History of significant infection or recurrent infection that, in the investigator's opinion, places the participant at risk by participating in this study.
  12. Receipt of a live-attenuated vaccine within 3 months of study enrollment.
  13. End-stage renal disease (eGFR <20 mL/min/1.73m<sup>2</sup>)
  14. Concomitant malignancies or a history of malignancy, with the exception of adequately treated basal and squamous cell carcinoma of the skin, or carcinoma in situ of the cervix.
  15. History of transplantation.
  16. History of primary immunodeficiency.
  17. Pregnancy.
  18. Breastfeeding.
  19. Unwillingness to use an FDA-approved form of birth control (including but not limited to a diaphragm, an intrauterine device, progesterone implants or injections, oral contraceptives, the double-barrier method, or a condom).
  20. Use of cyclophosphamide within the past 6 months.
  21. Use of anti-TNF medication, other biologic medications, or non-biologic experimental therapeutic agents within the past 90 days, or 5 half-lives prior to screening, whichever is greater.
  22. Intravenous immunoglobulin (IVIG), plasmapheresis, or leukopheresis within the past 90 days.
  23. Use of an investigational biologic agent within the past 6 months.
  24. Prior treatment with rituximab.
  25. Treatment with other biologic B cell therapy within the past 12 months.
  26. Liver function test (aspartate aminotransferase [AST], alanine

aminotransferase [ALT], or alkaline phosphatase) results that are  $\geq 2$  times the upper limit of normal.

27. Severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, pulmonary, cardiac, or neurological disease, either related or unrelated to SLE, with the exception of active lupus nephritis (or, in the investigator's opinion, any other concomitant medical condition that places the participant at risk by participating in this study).
28. Comorbidities requiring corticosteroid therapy, including those which have required three or more courses of systemic corticosteroids within the previous 12 months.
29. Current substance abuse or history of substance abuse within the past year.
30. History of severe allergic or anaphylactic reactions to chimeric or fully human monoclonal antibodies.
31. History of anaphylactic reaction to parenteral administration of contrast agents.
32. Lack of peripheral venous access.
33. History of severe depression or severe psychiatric condition.
34. History of suicidal thoughts within the past 2 months or suicidal behavior within the past 6 months, or a significant suicide risk in the investigator's opinion.
35. Inability to comply with study and follow-up procedures.

## **2. INTRODUCTION**

This statistical analysis plan (SAP) only includes analyses related to the clinical endpoints outlined in the protocol. Mechanistic analyses will be performed at the Immune Tolerance Network (ITN), and a separate analysis plan will be created to detail the planned analyses. Relevant clinical data from the study will be submitted to the ITN Biomarker and Discovery Research (BDR) to augment the mechanistic analyses.

### 3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following analyses and reporting conventions will be used:

- Randomized treatment groups:
  - Rituximab/Cyclophosphamide (RC) treatment arm refers to the subjects who are randomized to be maintained on prednisone from week 4 through week 96.
  - Rituximab/Cyclophosphamide/Belimumab (RCB) treatment arm refers to the subjects who are randomized to receive IV belimumab at weeks 4, 6, 8 and then every 4 weeks through week 48 in addition to the prednisone maintenance. After week 48, subjects in the RCB treatment arm are maintained on prednisone through week 96.
- Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form “n (%)” Percentages will be rounded to one decimal place.
- Numeric variables will be summarized using n, mean, standard deviation (SD), median, minimum (min), maximum (max). The min/max will be reported at the same level of significant digits as original data. The mean and median will be reported at one more significant digit than the precision of the data, and SD will be reported at two more significant digits than the precision of the data.
- The median will be reported as the average of the two middle numbers if the dataset contains an even number of observations.
- Test statistics including *t* and *z* test statistics will be reported to two decimal places.
- *P*-values will be reported to three decimal places if greater than or equal to 0.001. If less than 0.001, the value will be reported as “<0.001.” A *p*-value can be reported as “1.000” only if it is exactly 1.000 without rounding. A *p*-value can be reported as “0.000” only if it is exactly 0.000 without rounding.

If departures from these general conventions are present in the specific evaluations section of this SAP, then those conventions will take precedence over these general conventions.

#### 4. ANALYSIS SAMPLES

**Modified intent to treat sample (MITT)** will be defined as all randomized participants who receive study regimen, as defined below:

- Receive 1 dose of Solumedrol
- Receive 1 dose of rituximab
- Receive 1 dose of cyclophosphamide (CTX)
- Receive 1 dose of belimumab if in the RCB Group

Any randomized subject who fails to meet any objectively measured entry criterion assessed prior to randomization will be excluded per the guidelines described for the “full analysis set” in ICH E9 Section V.5.2.1.

There is one MITT analysis population, and it will be used to provide summary statistics and compare the treatment groups at each of the protocol time points (i.e. weeks 24, 48 and 96).

**Per protocol samples (PP)** will be defined as follows:

**PP24:** Treated participants in the Modified ITT sample who receive study regimen through week 24 and meet the following criteria:

- Receive 2 doses each of Solumedrol, rituximab, and CTX
- Receive at least 80% of belimumab infusions if in the RCB Group

This analysis population will be used to provide summary statistics and compare the treatment groups for the PP analysis at week 24.

**PP48:** Treated participants in the PP24 sample who receive study regimen through week 48 and meet the following criteria:

- Receive at least 80% of belimumab infusions if in the RCB Group

This analysis population may be different than the PP24 analysis population and will be used to provide summary statistics and compare the treatment groups for the PP analysis at week 48.

**PP96:** Treated participants in the PP48 sample who receive study regimen through week 96.

This analysis population may be different than the PP24 and PP48 analysis populations and will be used to provide summary statistics and compare the treatment groups for the PP analysis at week 96.

The Study Management Team will review deviations from the protocol in a blinded listing including, for example, violations of entry criteria, departures from assigned treatment regimen, or administration of study procedures outside the specified visit windows. The panel may exclude subjects with serious protocol deviations from the Per protocol samples.

**Safety sample (SS)** will be defined as all participants who receive at least one dose of study treatment.

## 5. STUDY SUBJECTS

### 5.1 Disposition of Subjects

The disposition of all enrolled subjects will be summarized in tables and listed.

The numbers and percentages of subjects enrolled, randomized, in each analysis sample, and completing the treatment regimen, as well as reasons for early termination from the study will be presented by treatment group and overall. For subjects discontinuing study treatment early, the reasons for discontinuing study treatment early will also be presented. A CONSORT diagram will be prepared to graphically display the disposition changes by treatment group throughout the phases of the study. Disposition of all enrolled subjects will be listed by treatment group and subject.

### 5.2 Demographic and Other Baseline Characteristics

Summary descriptive statistics for baseline and demographic characteristics will be reported by treatment group and overall for the MITT sample. Characteristics to be summarized include:

- Demographics
  - Age
  - Race
  - Ethnicity
  - Sex
  - Body weight
- Duration of lupus nephritis (i.e time from onset of lupus nephritis to screening visit)
- Proportion of subjects with >1 year duration of lupus nephritis
- Lupus nephritis class according to International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification at screening
- Presence of active non-renal lupus (i.e. classification of A, B or C in any non-renal body system in BILAG 2004)
- Baseline laboratory assessments
  - Urine protein to creatinine ratio (UPCR) from a 24-hour collection
  - Serum albumin
  - Serum creatinine
  - eGFR
  - B cell counts
  - IgG levels
  - Proportion of subjects with UPCR > 3 from a 24-hour collection
  - Proportion of subjects with IgG < 450 mg/dL
  - Proportion of subjects with C3 hypocomplementemia (see section 7.3.6)
  - Proportion of subjects with C4 hypocomplementemia (see section 7.3.6)
  - Proportion of subjects with positive anti-dsDNA (see section 7.3.7)

Demographic and baseline characteristic data for all enrolled subjects will also be presented in a data listing by treatment group and subject.



## **6. STUDY OPERATIONS**

### **6.1 Protocol Deviations**

The number of major protocol deviations, the number of each type of deviation, the number of site level deviations and the number of consented subjects with at least one deviation will be summarized over all sites.

Protocol deviations will be sorted by site and subject, and listed with information such as type of deviation, date of occurrence, details of the deviation, steps taken to address the deviation, who identified the deviation, and whether the deviation met IRB reporting requirements.

### **6.2 Treatment Adherence**

Treatment adherence will be summarized for the MITT sample by treatment group and overall for rituximab, CTX and Solumedrol doses received during infusions administered prior to randomization. Treatment adherence will also be summarized for the MITT sample in the RCB treatment arm for belimumab infusions received from week 4 through week 48. The total number of infusions received by each subject will be calculated along with the percent of the expected infusions and total dose received for each study medication. Prednisone dose taken by subjects at major time points will be summarized by treatment group at week 12 for the MITT sample, at week 24 for the MITT and PP24 samples, at week 48 for the MITT and week 48 samples, and at week 96 for the MITT and PP96 samples. The proportion of subjects who are taking 10mg/day or less of prednisone will be summarized by treatment group at week 12 for the MITT sample, at week 24 for the MITT and PP24 samples, at week 48 for the MITT and week 48 samples, and at week 96 for the MITT and PP96 samples. Study drug administration data will be listed by treatment group and subject.

#### **6.2.1 Rituximab/Cyclophosphamide/Solumedrol**

Subjects will receive infusions by site personnel of Solumedrol 100mg, rituximab 1000mg, and CTX 750mg intravenously (IV) at week 0 and week 2.

The date and time of infusion, dose administered and information on missed infusions or dose reductions will be recorded by site staff at the time of infusion.

#### **6.2.2 Prednisone**

All enrolled subjects will self-administer oral doses of prednisone 40 mg/day for the first 2 weeks, starting at week 0. Prednisone will then be tapered until study week 12 to a dose of 10 mg/day. This dose will be continued until week 48. Between week 48 and week 96, prednisone may be further tapered. However, the rate of taper should not be greater than 1 mg every month, and the dose should not be tapered below 5 mg/day.

The start date, end date, dose administered and information on dose changes will be recorded by site staff in the dosing log.

#### **6.2.3 Belimumab**

Subjects randomized to the RCB treatment arm will receive infusions by site personnel of belimumab 10mg/kg at weeks 4, 6, 8, and then every 4 weeks through week 48.

The date and time of infusion, dose administered and information on missed infusions or dose reductions will be recorded by site staff at the time of infusion.

## 7. ENDPOINT EVALUATION

### 7.1 Overview of Efficacy Analysis Methods

#### 7.1.1 Multicenter Studies

Study subjects were recruited from 14 study sites. Study data will be analyzed as a whole. Because randomization was not stratified by clinical site, it will not be included as a covariate in the analyses.

#### 7.1.2 Assessment Time Windows

Visit 0 (week 0) must occur within 21 days of visit –1 (screening visit). All other scheduled study visits should occur within the time limits specified below:

Visits 1 (week 2) through visit 4 (week 8):  $\pm 2$  days

Visit 5 (week 12) through visit 14 (week 48):  $\pm 7$  days

Visit 15 (week 60) through visit 18 (week 96):  $\pm 14$  days

Randomized subjects who discontinue from the study treatment regimen, as described in section 5.6 of the protocol, will be asked to complete the early discontinuation visit (visit 18) assessments. Early discontinuation subjects will be asked to return for a follow-up assessment 30 days after the early discontinuation visit. The subject will then be asked to complete the visits at week 24, 36, 48, 72, and 96, if these visits have not already occurred, for safety follow up.

Data collected outside of the assessment time windows will not be excluded from the analyses.

Unscheduled visits may also be performed throughout the study to document any new symptoms. The results captured in any unscheduled visit will not be included in summary displays by visit, but will be displayed in any subject level plots over time and in listings. Early discontinuation visits are recorded in the database as an unscheduled visit but will be handled differently than other unscheduled visits. Early discontinuation visit evaluations will be applied to the closest scheduled missed visit for summary displays but will be labeled as an early discontinuation visit in listings.

#### 7.1.3 Summary of Primary and Secondary Efficacy Analysis Methods

**Table 7-2 Table of Endpoints and Analysis Methods**

Endpoint	Time Points	Analysis Samples	Analysis Methods
<b>Primary Endpoint Analysis</b>			
Proportion of subjects who experience at least one Grade 3 or higher infectious adverse event	Week 48	MITT, PP48	<ul style="list-style-type: none"> <li>95% confidence intervals by treatment group using Clopper-Pearson (exact) method for binomial proportions</li> <li>Logistic regression model on treatment group</li> </ul>

<b>Secondary Endpoints Analysis</b>			
Proportion of subjects who experience at least one Grade 3 or higher infectious adverse event	Weeks 24, 96	MITT, PP24, PP96	Same as primary endpoint
Proportion of subjects who experience at least one occurrence of Grade 4 hypogammaglobulinemia	Weeks 24, 48, 96	MITT, PP24, PP48, PP96	Same as primary endpoint
Proportion of subjects with B cell reconstitution	Weeks 24, 48, 96	MITT, PP24, PP48, PP96	Same as primary endpoint
Proportion of subjects who achieve a complete response	Weeks 24, 48, 96	MITT, PP24, PP48, PP96	Same as primary endpoint
Proportion of subjects who achieve an overall response	Weeks 24, 48, 96	MITT, PP24, PP48, PP96	Same as primary endpoint
Proportion of subjects who achieve a sustained complete response	Week 96	MITT, PP96	Same as primary endpoint
Proportion of subjects who experience treatment failure	Weeks 24	MITT	Same as primary endpoint
	Week 48	MITT, PP24	Same as primary endpoint
	Week 96	MITT, PP48	Same as primary endpoint
Proportion of subjects who have a negative anti-dsDNA result	Weeks 24, 48, 96	MITT, PP24, PP48, PP96	Same as primary endpoint
Proportion of subjects who are hypocomplementemic	Weeks 24, 48, 96	MITT, PP24, PP48, PP96	Same as primary endpoint
Frequency of non-renal flares	Weeks 24, 48, 96	MITT, PP24, PP48, PP96	<ul style="list-style-type: none"> <li>Pearson's chi-square test by treatment group (or Fisher's exact test by treatment group for small sample sizes)</li> </ul>

## 7.2 Primary Endpoint

### 7.2.1 Computation of the Primary Endpoint

The primary endpoint is the proportion of subjects who experience at least one Grade 3 or higher treatment-emergent infectious adverse event (G3IAE) at or prior to week 48.

All adverse events (AEs) will be classified by system organ class and preferred term, according to the Medical Dictionary for Regulatory Activities [MedDRA] version 17.0. The severity of AEs will be classified using the National Cancer Institute's (NCI's) Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03. Each AE is entered on the electronic case report form (eCRF) once at the highest severity. AEs will

be collected from screening through study termination. Treatment-emergent AEs will be identified as those with an onset date on or after the first dose of study medication as well as those with onset before first dose but that continued and worsened in severity after first dose. If the start of the AE in relation to the start of study medication cannot be established (e.g., the start date for the AE is missing), then the AE will be considered treatment-emergent.

The study team will review the MedDRA body systems and preferred terms of all Grade 3 or higher adverse events to determine if they are infectious adverse events.

### **7.2.2 Primary Analysis of the Primary Endpoint**

The primary analysis for the primary endpoint will be performed on the MITT sample and is designed to provide point estimates and confidence intervals for the proportion of subjects in each treatment arm who experience at least one Grade 3 or higher treatment-emergent infectious adverse event (G3IAE) at or prior to week 48.

The 95% confidence interval bounds for the proportion estimates in each treatment group will be calculated using the Clopper-Pearson (exact) method for binomial proportions.

### **7.2.3 Secondary Analyses of the Primary Endpoint**

The primary analysis method described above will be repeated using the PP48 sample, if different from the MITT sample.

Additional analyses will be performed to compare the proportions of subjects between the two treatment arms by a logistic regression model with an indicator of whether the subject experienced at least one G3IAE as the dependent variable and treatment group as the independent variable. The logistic regression analysis will be performed on the MITT and PP48 samples.

The confidence intervals and logistic regression analyses will be repeated on the proportion of subjects who experience at least one post-randomization G3IAE at or prior to week 48. Post-randomization AEs are defined as those occurring on or after the subject's week 4 visit. The analyses on the proportions of subjects who experience at least one post-randomization G3IAE at or prior to week 48 will be performed on the MITT and PP48 samples.

## **7.3 Secondary Endpoints and Analyses**

The secondary analyses will support the primary analysis by providing a deeper understanding of events. P-values for all inferential analyses will be presented as a description of strength of evidence of relationships rather than tests of hypotheses. As such, no corrections for multiplicity are planned.

Listings will be prepared for all efficacy assessments with the subjects in the MITT sample. All efficacy listings will be sorted in order of treatment group, subject identifier, and time of assessment (e.g., visit, time, and/or event).

### **7.3.1 Grade 3 or Higher Infectious Adverse Events**

In addition to the primary and secondary analyses for the primary endpoint, the following analyses on G3IAEs are planned:

- The proportion of subjects who experienced at least one G3IAE at or prior to week 24 will be analyzed using a logistic regression model similar to the one used in the primary endpoint analysis. The 95% confidence interval bounds for the proportion estimates in each treatment group will also be calculated using the Clopper-Pearson (exact) method. The week 24 analysis will be performed on the MITT and PP24 samples. The analyses for week 24 will also be repeated for week 96 using the MITT and PP96 samples.
- The proportion of subjects who experienced at least one post-randomization G3IAE at or prior to week 24 will be analyzed using a logistic regression model similar to the one used in the primary endpoint analysis. The 95% confidence interval bounds for the proportion estimates in each treatment group will also be calculated using the Clopper-Pearson (exact) method. The week 24 analysis will be performed on the MITT and PP24 samples. The analyses for week 24 will also be repeated for week 96 using the MITT and PP96 samples.

### 7.3.2 Hypogammaglobulinemia

Hypogammaglobulinemia will be assessed throughout the subject's study participation. Blood samples will be collected from subjects at every visit to assess IgG levels. An adverse event of Grade 4 hypogammaglobulinemia will be reported by the site if a subject has an IgG test result  $< 300$  mg/dL that is associated with a G3IAE. The following analyses are planned:

- The proportion of subjects who experienced at least one event of Grade 4 hypogammaglobulinemia at or prior to week 24 will be analyzed using a logistic regression model similar to the one used in the primary endpoint analysis. The 95% confidence interval bounds for the proportion estimates in each treatment group will also be calculated using the Clopper-Pearson (exact) method. The week 24 analysis will be performed on the MITT and PP24 samples. The analyses for week 24 will be repeated for week 48 using the MITT and PP48 samples, and at week 96 using the MITT and PP96 samples.
- IgG level at week 24 will be analyzed using an analysis of covariance model (ANCOVA) with the IgG level as the dependent variable, urine protein-to-creatinine ratio (UPCR) based on a 24-hour collection at week 24 as the independent variable and treatment group as a covariate. The week 24 analysis will be performed on the MITT and PP24 samples. The analyses for week 24 will be repeated for week 48 using the MITT and PP48 samples, and at week 96 using the MITT and PP96 samples.
- IgG level at week 24 will be plotted against the 24-hour UPCR at week 24 by treatment group for the MITT and PP24 samples. The figures for week 24 will be repeated for week 48 using the MITT and PP48 samples, and at week 96 using the MITT and PP96 samples.

### 7.3.3 B cells

Blood samples will be collected from subjects at weeks 0, 12, 24, 36, 48, 60, 72, 84 and 96 to assess B cell levels. B cell reconstitution is defined as a B cell count that is greater than or equal to the subject's baseline B cell count, or the lower limit of normal for the laboratory test, whichever is lower. The following analyses are planned:

- The proportion of subjects who achieved B cell reconstitution at week 24 will be analyzed using a logistic regression model similar to the one used in the primary endpoint analysis. The 95% confidence interval bounds for the proportion estimates in each treatment group will also be calculated using the Clopper-Pearson (exact) method. The week 24 analysis will be performed on the MITT and PP24 samples. The analyses for week 24 will be repeated for week 48 using the MITT and PP48 samples, and at week 96 using the MITT and PP96 samples.
- B cell count at week 24 will be analyzed using an analysis of covariance model (ANCOVA) with the B cell count as the dependent variable, IgG level at week 24 as the independent variable and treatment group as a covariate. The week 24 analysis will be performed on the MITT and PP24 samples. The analyses for week 24 will be repeated for week 48 using the MITT and PP48 samples, and at week 96 using the MITT and PP96 samples.
- B cell count at week 24 will be plotted against the IgG level at week 24 by treatment group for the MITT and PP24 samples. The figures for week 24 will be repeated for week 48 using the MITT and PP48 samples, and at week 96 using the MITT and PP96 samples.
- 

### 7.3.4 Response to Treatment

Response to treatment will be assessed at screening (visit -1) and weeks 12, 24, 36, 48 and 96.

Complete response is defined as meeting all of the following criteria:

- Urine protein-to-creatinine ratio (UPCR)  $< 0.5$ , based on a 24-hour collection
- Estimated glomerular filtration rate (eGFR)  $\geq 120$  ml/min/1.73m<sup>2</sup> calculated by the CKD-EPI formula (Levey, et al., 2009) or, if  $< 120$  ml/min/1.73m<sup>2</sup>, then  $> 80\%$  of eGFR at screening.
- Prednisone dose tapered to 10 mg/day, or as specified in section 5.5.2 of the protocol

Overall response is defined as meeting all of the following criteria:

- $> 50\%$  improvement in the UPCR from screening, based on a 24-hour collection
- Estimated glomerular filtration rate (eGFR)  $\geq 120$  ml/min/1.73m<sup>2</sup> calculated by the CKD-EPI formula (Levey, et al., 2009) or, if  $< 120$  ml/min/1.73m<sup>2</sup>, then  $> 80\%$  of eGFR at screening.

- Prednisone dose tapered to 10 mg/day, or as specified in section 5.5.2 of the protocol

Sustained complete response is defined as achieving complete response at both week 48 and week 96

Partial response is defined as meeting the criteria for overall response, but not meeting the criteria for complete response.

Non-response is defined as not meeting the overall response criteria.

The following analyses are planned:

- The proportion of subjects who achieved complete response at week 24 will be analyzed using a logistic regression model similar to the one used in the primary endpoint analysis. The 95% confidence interval bounds for the proportion estimates in each treatment group will also be calculated using the Clopper-Pearson (exact) method. The week 24 analysis will be performed on the MITT and PP24 samples. The analyses for week 24 will be repeated for week 48 using the MITT and PP48 samples, and at week 96 using the MITT and PP96 samples.
- The proportion of subjects who achieved overall response at week 24 will be analyzed using a logistic regression model similar to the one used in the primary endpoint analysis. The 95% confidence interval bounds for the proportion estimates in each treatment group will also be calculated using the Clopper-Pearson (exact) method. The week 24 analysis will be performed on the MITT and PP24 samples. The analyses for week 24 will be repeated for week 48 using the MITT and PP48 samples, and at week 96 using the MITT and PP96 samples.
- The proportion of subjects who achieved sustained complete response at week 96 will be analyzed using a logistic regression model similar to the one used in the primary endpoint analysis. The 95% confidence interval bounds for the proportion estimates in each treatment group will also be calculated using the Clopper-Pearson (exact) method. The week 96 analysis will be performed on the MITT and PP96 samples.
- The numbers and percentages of subjects who achieved complete response and of subjects who achieved an overall response at week 24 will be presented by race and treatment group on the MITT and PP24 samples. The analyses for week 24 will be repeated for week 48 using the MITT and PP48 samples, and at week 96 using the MITT and PP96 samples.
- The numbers and percentages of subjects who achieved complete response , partial response and non-response at week 24 will be analyzed using a Fisher's exact test by treatment group on the MITT and PP24 samples. The analyses for week 24 will be repeated for week 48 using the MITT and PP48 samples, and at week 96 using the MITT and PP96 samples.



### 7.3.5 Treatment Failure

Subjects may be discontinued from the protocol treatment regimen at any point during the study if any of the criteria for treatment discontinuation specified in section 5.6 of the protocol are met.

Treatment failure is defined as discontinuation from the protocol treatment regimen due to worsening nephritis, infection or study medication toxicity. The Study Management Team will review treatment discontinuation reasons in a blinded listing to determine which treatment discontinuation reasons are indicative of renal treatment failure or non-renal treatment failure.

The following analyses are planned:

- The proportion of subjects who met the criteria for treatment failure at or prior to week 24 will be analyzed using a logistic regression model similar to the one used in the primary endpoint analysis. The 95% confidence interval bounds for the proportion estimates in each treatment group will also be calculated using the Clopper-Pearson (exact) method. The week 24 analysis will be performed on the MITT sample. The analyses for week 24 will be repeated for week 48 using the MITT sample, and at week 96 using the MITT and PP96 samples.
- The proportion of subjects who met the criteria for renal treatment failure at or prior to week 24 will be analyzed using a logistic regression model similar to the one used in the primary endpoint analysis. The 95% confidence interval bounds for the proportion estimates in each treatment group will also be calculated using the Clopper-Pearson (exact) method. The week 24 analysis will be performed on the MITT sample. The analyses for week 24 will be repeated for week 48 using the MITT sample, and at week 96 using the MITT and PP96 samples.
- The proportion of subjects who met the criteria for non-renal treatment failure at or prior to week 24 will be analyzed using a logistic regression model similar to the one used in the primary endpoint analysis. The 95% confidence interval bounds for the proportion estimates in each treatment group will also be calculated using the Clopper-Pearson (exact) method. The week 24 analysis will be performed on the MITT sample. The analyses for week 24 will be repeated for week 48 using the MITT sample, and at week 96 using the MITT and PP96 samples.

### 7.3.6 Hypocomplementemia

Blood samples will be collected from subjects at weeks 0, 4 and every visit from week 8 through 96 to assess levels of C3 and C4. A subject will be classified as having hypocomplementemia for C3 if the C3 level is lower than the lower limit of normal for the laboratory test. A subject will be classified as having hypocomplementemia for C4 if the C4 level is lower than the lower limit of normal for the laboratory test. The following analyses are planned:

- The proportion of subjects who are hypocomplementemic for C3 at week 24 will be analyzed using a logistic regression model similar to the one used in the

primary endpoint analysis. The 95% confidence interval bounds for the proportion estimates in each treatment group will also be calculated using the Clopper-Pearson (exact) method. The week 24 analysis will be performed on the MITT and PP24 samples. The analyses for week 24 will be repeated for week 48 using the MITT and PP48 samples, and at week 96 using the MITT and PP96 samples.

- The proportion of subjects who are hypocomplementemic for C4 at week 24 will be analyzed using a logistic regression model similar to the one used in the primary endpoint analysis. The 95% confidence interval bounds for the proportion estimates in each treatment group will also be calculated using the Clopper-Pearson (exact) method. The week 24 analysis will be performed on the MITT and PP24 samples. The analyses for week 24 will be repeated for week 48 using the MITT and PP48 samples, and at week 96 using the MITT and PP96 samples.
- The proportion of subjects who are not hypocomplementemic for C3 at week 24, out of subjects who were hypocomplementemic for C3 at baseline, will be analyzed using a logistic regression model similar to the one used in the primary endpoint analysis. The 95% confidence interval bounds for the proportion estimates in each treatment group will also be calculated using the Clopper-Pearson (exact) method. The week 24 analysis will be performed on the MITT and PP24 samples. The analyses for week 24 will be repeated for week 48 using the MITT and PP48 samples, and at week 96 using the MITT and PP96 samples.
- The proportion of subjects who are not hypocomplementemic for C4 at week 24, out of subjects who were hypocomplementemic for C4 at baseline, will be analyzed using a logistic regression model similar to the one used in the primary endpoint analysis. The 95% confidence interval bounds for the proportion estimates in each treatment group will also be calculated using the Clopper-Pearson (exact) method. The week 24 analysis will be performed on the MITT and PP24 samples. The analyses for week 24 will be repeated for week 48 using the MITT and PP48 samples, and at week 96 using the MITT and PP96 samples.
- The proportion of subjects who are not hypocomplementemic for C3 and C4 at week 24, out of subjects who were hypocomplementemic for C3 or C4 at baseline, will be analyzed using a logistic regression model similar to the one used in the primary endpoint analysis. The 95% confidence interval bounds for the proportion estimates in each treatment group will also be calculated using the Clopper-Pearson (exact) method. The week 24 analysis will be performed on the MITT and PP24 samples. The analyses for week 24 will be repeated for week 48 using the MITT and PP48 samples, and at week 96 using the MITT and PP96 samples.

### **7.3.7 Anti-dsDNA**

Blood samples will be collected from subjects at weeks 0, 4 and every visit from week 8 through 96 to assess levels of anti-dsDNA. A subject will be classified as having

negative anti-dsDNA if the test result is within normal range. The following analyses are planned:

- The proportion of subjects who have a negative anti-dsDNA result at week 24 will be analyzed using a logistic regression model similar to the one used in the primary endpoint analysis. The 95% confidence interval bounds for the proportion estimates in each treatment group will also be calculated using the Clopper-Pearson (exact) method. The week 24 analysis will be performed on the MITT and PP24 samples. The analyses for week 24 will be repeated for week 48 using the MITT and PP48 samples, and at week 96 using the MITT and PP96 samples.
- The proportion of subjects who have a negative anti-dsDNA result at week 24, out of subjects who had a positive anti-dsDNA result at baseline, will be analyzed using a logistic regression model similar to the one used in the primary endpoint analysis. The 95% confidence interval bounds for the proportion estimates in each treatment group will also be calculated using the Clopper-Pearson (exact) method. The week 24 analysis will be performed on the MITT and PP24 samples. The analyses for week 24 will be repeated for week 48 using the MITT and PP48 samples, and at week 96 using the MITT and PP96 samples.

### **7.3.8 Non-renal Flares/BILAG**

British Isles Lupus Assessment Group (BILAG) assessments will be evaluated at weeks 0, 4 and every visit from week 8 through 96. A non-renal flare is defined as any new “A” finding in a non-renal organ system according to the BILAG 2004 guidelines (Isenberg, et al., 2005) that occurs after week 0. The BILAG “A” finding represents a significant increase in, or new manifestation of, lupus disease activity. The following analyses are planned:

- The frequency of non-renal flares at or prior to week 24 will be analyzed using a Pearson’s chi-square test by treatment group. If the number of non-renal flares at or prior to week 24 is small, Fisher’s exact test will be used in place of the Pearson’s chi-square test. The week 24 analysis will be performed on the MITT and PP24 samples. The analyses for week 24 will be repeated for week 48 using the MITT and PP48 samples, and at week 96 using the MITT and PP96 samples.

### **7.3.9 Exploratory analyses**

Additional exploratory analyses are planned to assess renal status.

- 

1. UPCR < 0.8, based on a 24-hour collection

The following analyses are planned:

- The proportion of subjects who achieved UPCR <0.8 at week 48 will be analyzed using a logistic regression model similar to the one used in the primary endpoint analysis. The 95% confidence interval bounds for the proportion estimates in each treatment group will also be calculated using the Clopper-Pearson (exact) method. The week 48 analysis will be performed on the MITT and PP48 samples.

2. Percent change in UPCR from screening, based on a 24-hour collection

The following analyses are planned:

- The percent change in UPCR from screening, based on a 24-hour collection will be summarized at week 24 for the MITT and PP24 samples, at week 48 for the MITT and PP48 samples, and at week 96 for the MITT and PP96 samples.

## 8. SAFETY EVALUATION

### 8.1 Overview of Safety Analysis Methods

All safety analyses will be carried out using the safety sample defined in Section 4 unless otherwise noted. Missing safety information will not be imputed. These analyses will not be stratified by site.

Listings will be prepared for all safety assessments with the subjects in the safety sample. All safety listings will be sorted in order of treatment group, subject identifier, and time of assessment (e.g., visit, time, and/or event).

### 8.2 Adverse Events

All AEs will be classified by system organ class and preferred term, according to the Medical Dictionary for Regulatory Activities (MedDRA) version 17.0. The severity of AEs will be classified using the National Cancer Institute's (NCI's) Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03. Each AE is entered on the electronic case report form (eCRF) once at the highest severity. AEs will be collected from screening through study termination. Treatment-emergent AEs will be identified as those with an onset date on or after the first dose of study medication as well as those with onset before first dose but that continued and worsened in severity after first dose. If the start of the AE in relation to the start of study medication cannot be established (e.g., the start date for the AE is missing), then the AE will be considered treatment-emergent. All data tabulations will be of only treatment-emergent events while non-treatment-emergent AEs will be included in the listings.

An overall summary table will present the number of events and the number and percentage of subjects having at least one event in the following categories by treatment group and overall for treatment-emergent AEs through the end of treatment. End of treatment for AE summaries is defined as 30 days after the date the subject discontinues the study treatment regimen. :

- AEs
- AEs indicated as serious
- AEs that lead to study drug discontinuation
- AEs that were reported as being related to a study drug
- AEs reported by severity

An additional overall summary table will present post-randomization AEs for the above categories through the end of treatment.

An additional overall summary table will present post-treatment AEs for the above categories. Post-treatment AEs are defined as AEs with an initiation date after the end of treatment.

Any treatment-emergent AEs that are classified in the following categories will be considered AEs of interest:

- Any event leading to death (Grade 5)

- Grade 2 or greater leukopenia or thrombocytopenia
- Premature ovarian failure
- Malignancy
- Venous thromboembolic event (deep venous thrombosis or pulmonary embolism)
- Disease- or study medication-related event leading to hospitalization
- Infusion reactions (within 24 hours of infusion) that result in the cessation of further infusions (including cytokine-release allergic reaction)

For AEs of interest, the number of events and the number and percentage of subjects having at least one event at or prior to week 24 for each category will be summarized by treatment group and overall. Additional summary tables of AEs of interest will also be presented for events at or prior to week 48, and for events at or prior to week 96.

In addition, AEs classified by MedDRA system organ class and preferred term will be summarized by treatment group and overall for each of the following:

- All AEs
- AEs by severity
- AEs by relationship to study drug

Separate data listings will be provided for treatment-related AEs and AEs leading to study drug discontinuation.

### **8.3 Deaths and Serious Adverse Events**

Serious adverse events (SAEs) will be listed by treatment group and subject. If any subjects die, a listing will be created and will include the primary cause of death and time to death.

### **8.4 Pregnancies**

Pregnancies that occurred in enrolled subjects during study participation will be listed by treatment group and subject. The listing will include date of last menstrual period, expected date of delivery, and date and type of pregnancy outcome.

### **8.5 Clinical Laboratory Evaluation**

Clinical laboratory measurements include serum chemistry, hematology, anti-dsDNA, ANA, complements, B cells, anticardiolipin antibodies, quantitative serum immunoglobulins, anti-ENA, 24-hour urine chemistry, spot urine chemistry, and urinalysis. Results will be converted to standardized units where possible.

The following analyses are planned:

- Laboratory data will be plotted by treatment group for the Safety sample to show patterns over time. Summary statistics including 25<sup>th</sup> percentile, median, and 75<sup>th</sup> percentile will be plotted for each visit by treatment group. Lines connecting individual subject results from subjects with grade 2 or higher values will be

overlaid on each figure. For lab results that are not gradable, results from subjects with values outside of 2 \*upper limit of normal or 0.5\*lower limit of normal will be overlaid. Tests with qualitative results (such as “present” or “positive”) will not be plotted.

- Laboratory data will be plotted by treatment group for the MITT sample to show patterns over time. Summary statistics including 25<sup>th</sup> percentile, median, and 75<sup>th</sup> percentile will be plotted for each visit by treatment group. Lines connecting individual subject results from subjects with grade 2 or higher values will be overlaid on each figure. For lab results that are not gradable, results from subjects with values outside of 2 \*upper limit of normal or 0.5\*lower limit of normal will be overlaid. Tests with qualitative results (such as “present” or “positive”) will not be plotted. Data presented in the figures will be censored after the subject has been discontinued from study treatment regimen.
- Change in laboratory results from baseline at each laboratory collection visit will be summarized by treatment group and overall for the Safety and MITT samples.

## **8.6 Vital Signs, Physical Findings, and Other Observations Related to Safety**

### **8.6.1 Vital Signs**

Vital sign results will be plotted by treatment group to show patterns over time. Summary statistics including 25th percentile, median, and 75th percentile will be plotted for each visit. Lines connecting individual subject results from subjects with grade 2 or higher values will be overlaid on each figure. Vital signs collected during infusions will be presented in a separate listing by treatment group, subject and time point.

### **8.6.2 Physical Examinations**

Physical examination results of normal, abnormal, and not done will be summarized as frequencies and percentages by body system and visit by treatment group and overall. Body systems classified as abnormal in the physical exams will be listed.

## **9. OTHER ANALYSES**

### **9.1 Use of Medications**

Medications will be coded according to the World Health Organization (WHO) Drug Dictionary (version V2014.01). The number and percentage of subjects receiving prior and concomitant medications will be presented overall and by medication class. When reporting the number of subjects receiving the medication, a subject will only be counted once if they ever received the medication within the medication class. Percentages will be based on the number of subjects in the safety sample. Concomitant medications will be presented in a data listing and prohibited medications will be flagged. Medications that were started prior to week 0 will be denoted with an asterisk.

### **9.2 Medical History**

Body systems classified as abnormal in the medical history eCRF will be listed by treatment group, subject and body system.



## **10. INTERIM ANALYSES AND DATA MONITORING**

The progress of the study will be monitored by the Autoimmune Data and Safety Monitoring Board (DSMB). The Autoimmune DSMB will be chartered to review safety data and to make recommendations regarding continuation, termination, or modification of the study. The DSMB will formally review the safety data at least yearly. The discontinuation of study treatment will also be periodically reported to the DSMB.

In addition, safety data will be reviewed by the DSMB when an event occurs that is of sufficient concern to the National Institute of Allergy and Infectious Diseases (NIAID) medical monitor or protocol chair to warrant review, or when an event occurs that could contribute to a predefined stopping rule specified in the protocol.

## **11. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL**

### **11.1 Analysis populations**

The definition for Per protocol 96 sample (PP96) was modified from the definition in protocol version 2.0. The definition of PP96 in the protocol is:

**PP96:** Treated participants in the PP48 sample who continue in the study beyond 48 weeks.

The definition for the PP96 sample was revised so that it includes subjects who complete the full study on the study treatment regimen, instead of subjects who continue on the study treatment regimen beyond week 48. The revised definition for PP96 sample in this Statistical Analysis Plan is:

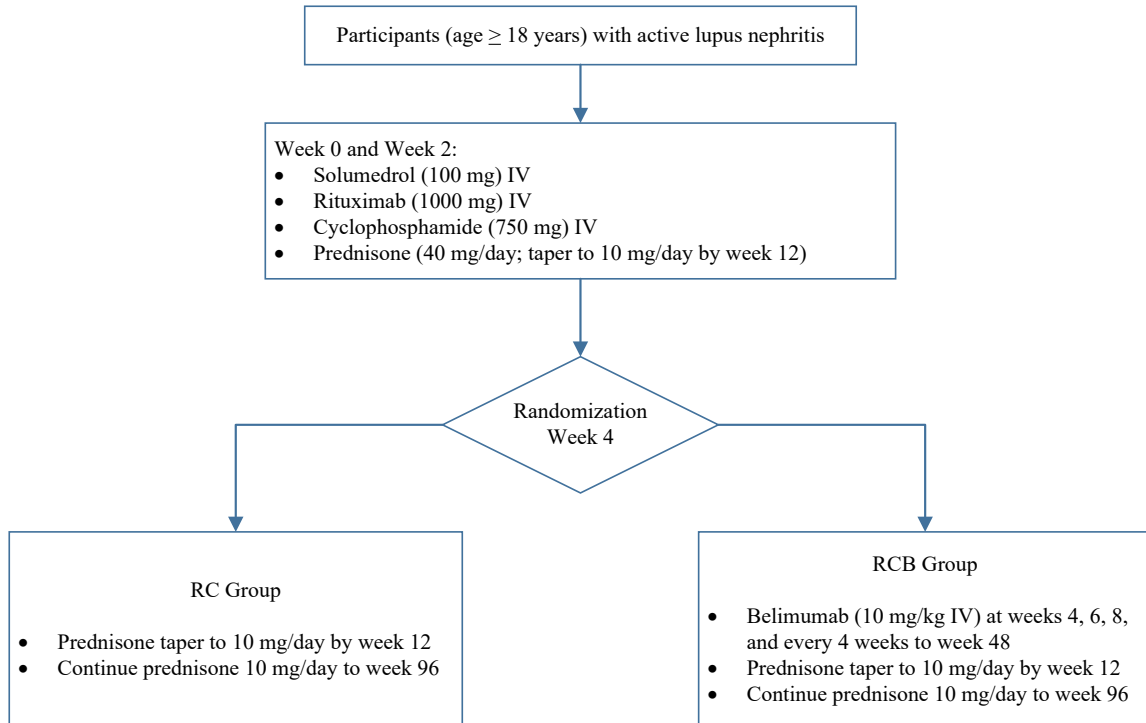
**PP96:** Treated participants in the PP48 sample who receive study regimen through week 96.

## 12. REFERENCES

- Isenberg, D. A., Rahman, A., Allen, E., Farewell, V., Akil, M., Bruce, I. N., et al. (2005). BILAG 2004. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. *Rheumatology (Oxford, England)*, 902-6.
- Levey, A. S., Stevens, L. A., Schmid, C. H., Zhang, Y. L., Castro, A. F., Feldman, H. I., et al. (2009). A new equation to estimate glomerular filtration rate. *Annals of internal medicine*, 604-12.

## 13. APPENDICES

### 13.1 Study Flow Chart



### 13.2 Schedule of Events

Study Week		0	2	4	6	8	12	16	20	24	28	32	36	40	44	48	60	72	84	96		U <sup>1</sup>
Visit Number	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		U
<b>General Assessments</b>																						
Informed consent	x																					
Randomization				x																		
Medical history	x																					
Lupus history	x																					
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Comprehensive physical examination	x																					
Limited physical examination		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
<b>Study Drug Administration</b>																						
Diphenhydramine		x	x																			
Acetaminophen		x	x																			
Solunedrol		x	x																			
Rituximab		x	x																			
Cyclophosphamide		x	x																			
Belimumab <sup>2</sup>				x	x	x	x	x	x	x	x	x	x	x	x	x						
Prednisone <sup>3</sup>		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
<b>Clinical Laboratory Assessments</b>																						
Hematology	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum creatinine	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum chemistry	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum albumin	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum urea nitrogen	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum pregnancy	x																					
Spot urine	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
24-hour urine	x						x			x			x			x					x	x
Urinalysis	x	x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
STAT urine pregnancy		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ANA	x															x					x	
HIV	x																					
Hepatitis B	x																					
Hepatitis C	x																					
Chest x-ray	x																					

<sup>1</sup> U= unscheduled visit

<sup>2</sup> Belimumab administered only to the RCB group as outlined in section 3.1

<sup>3</sup> Taken daily. First dose will be administered the day following Visit 0. Methylprednisolone may be substituted for prednisone in equivalent doses, at the discretion of the investigator.

Study Week		0	2	4	6	8	12	16	20	24	28	32	36	40	44	48	60	72	84	96		U <sup>1</sup>
Visit Number	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		U
Anti-dsDNA	x	x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
C3, C4		x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
CD19		x					x			x			x			x	x	x	x	x		
Anticardiolipin Ab (IgA, IgG, and IgM)		x								x						x						
Quantitative serum immunoglobulins (IgA, IgG, and IgM)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Anti-ENA (anti-Sm and anti-RNP)		x								x						x				x		
QuantiFERON - TB Gold test <sup>4</sup>	x																					
<b>Lupus Assessments</b>																						
BILAG-2004		x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
SELENA-SLEDAI		x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
SLICC		x								x						x		x		x		
<b>Clinical Pathology Assessment</b>																						
Kidney biopsy <sup>5</sup>	x																					
<b>Mechanistic Laboratory Assessments<sup>6</sup></b>																						
Whole blood autoreactive B cell frequency		x					x			x			x			x	x	x	x	x		
Whole blood flow cytometry panel staining		x					x			x			x			x	x	x	x	x		
Whole blood gene expression profiling		x					x			x			x			x	x	x	x	x		
Serum secreted cytokines		x					x			x			x			x	x	x	x	x		
Genotyping		x																				
Antibody to John Cunningham virus		x																				
Urine studies		x					x			x			x			x	x	x	x	x		

<sup>4</sup> PPD tuberculin test may be substituted for QuantiFERON – TB Gold test.

<sup>5</sup> If clinically indicated.

<sup>6</sup> Perform only when Hgb  $\geq$  8 g/dL at previous visit.