Official Title: **A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Evaluate the Safety and Efficacy of Obinutuzumab in Patients with ISN/RPS 2003 Class III OR IV Lupus Nephritis**

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STATISTICAL ANALYSIS PLAN

TITLE:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF OBINUTUZUMAB IN PATIENTS WITH ISN/RPS 2003 CLASS III OR IV LUPUS NEPHRITIS**
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STATISTICAL ANALYSIS PLAN APPROVAL

Name	Reason for Signing	Date and Time (UTC)
[redacted]	Company Signatory	17-Aug-2018 08:29:54

TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

1. BACKGROUND

Study WA29748 (NOBILITY) is a Phase II, parallel-group, double-blind, randomized, placebo-controlled study that aims to evaluate the efficacy and safety of obinutuzumab plus mycophenolate mofetil (MMF) with placebo plus MMF in patients with Class III or IV lupus nephritis (LN). The study consists of three periods: a screening period, a 104-week, double-blinded, treatment period followed by an additional B-cell follow-up (BCFU) period extending until patients have achieved their baseline cluster of differentiation (CD)19 level or the lower limit of normal (LLN) of $CD19^+$ B cells.

This Statistical Analysis Plan (SAP) describes the statistical methodology and data handling rules to be used for the Week 52 primary endpoint analysis. The primary reporting event will include all data up to Week 52 or early withdrawal, and will contribute towards a regulatory submission.

Treatment period data will be locked after all patients have completed the Week 52 visit.

A second reporting event will occur after all patients complete the Week 104 visit or withdraw early from the study. A final reporting event and study database lock will occur after all patients complete the treatment and (if applicable) BCFU period or withdraw early from BCFU. Details of these subsequent reporting events will be documented in a separate SAP or specification document.

2. STUDY DESIGN

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is provided in Appendix 1. Additional details including the study flowchart and schedule of assessments (Appendix 2) can be found in the study protocol (version 3.0; 2 February 2016).

2.2 OUTCOME MEASURES

2.2.1 Primary Efficacy Outcome Measures

The proportion of patients who achieve complete renal response (CRR) will be evaluated at 52 weeks.

2.2.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures are as follows:

- Proportion of patients who achieve an overall response at Week 52 (CRR + partial renal response [PRR])
- Proportion of patients that achieve a modified CRR (mCRR1) at Week 52 employing the primary−efficacy measure definition and removing the urinary sediment analysis criteria
- Proportion of patients that achieve a second modified CRR (mCRR2) at Week 52

- Time to CRR, over the course of 52 weeks.
- Time to overall response (CRR + PRR) over the course of 52 weeks
- Percent change from baseline and absolute assessments of biomarkers of LN disease activity (e.g., reduction in anti-dsDNA antibody levels, increase C3 and C4 levels)
- Proportion of patients that achieve a PRR at Week 52
- Proportion of patients who achieve a CRR at Week 24
- Proportion of patients that achieve a third modified CRR (mCRR3) at Week 52

2.2.3 Safety Outcome Measures

The safety outcome measures are as follows:

- Incidence, type, and severity of adverse events (AEs) and adverse events of special interest (AESI), including infusion reactions, infections, thrombocytopenia, and neutropenia
- Proportion of patients with abnormal vital signs
- Proportion of patients with abnormal laboratory values

Safety will be monitored through regular physical examinations, vital signs, hematologic and chemistry laboratory tests, urinalyses, and incidence and severity of AEs.

In addition, the following will be examined:

- Circulating B cells, T cells, neutrophils, and other cell populations
- Plasma immunoglobulins (total Ig, IgG, IgM, and IgA)
- Record of menses
- Pregnancy
- Antibody titers for mumps, rubella, varicella, tetanus, influenza, and *Streptococcus pneumoniae*

2.2.4 Exploratory Outcome Measures

The exploratory outcome measures are as follows (based on data availability):

- Absolute and percent change in urine protein creatinine ratio (UPCR) from baseline ~~at~~ to Week 52
- Changes in levels of circulating B-cell subsets relative to baseline
- Changes in levels of exploratory biomarkers, which may include but are not limited to levels of protein and mRNA in serum, plasma, blood, and urine, relative to baseline
- Proportion of patients experiencing a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)-2K flare
- Proportion of patients experiencing an extrarenal flare over 52 weeks

- Proportion of patients experiencing a renal flare over 52 weeks and 104 weeks
- Proportion of patients achieving CRR, mCRR1, mCRR2, and mCRR3 at additional timepoints, including Week 12, Week 24, and Week 36
- Physician's Global Assessment of disease activity
- Subject's Global Assessment of disease activity
- Glucocorticoid Toxicity Change Index (GTCI)
- Renal biopsy evaluations
- Time to mCRR1, mCRR2, and mCRR3 over the course of 52 weeks
- Changes in Systemic Lupus Erythematosus Disease Activity Index-2K (SLEDAI-2K) relative to baseline
- Proportion of patients who receive rescue therapy
- Proportion of patients who achieve each of the components of the primary endpoint

2.3 DETERMINATION OF SAMPLE SIZE

The primary efficacy endpoint of this study is the proportion of patients that achieve CRR. It is estimated that approximately 30% of patients with proliferative LN who are receiving MMF (or equivalent) will achieve a CRR at Week 52 and that the addition of obinutuzumab to MMF (or equivalent) will induce an overall CRR rate of 50% at Week 52. On the basis of these assumptions, a total of 120 patients randomized to obinutuzumab- and placebo-treated groups in a 1:1 ratio (60 patients in each of the obinutuzumab- and placebo-treated groups) will yield approximately 83% power at the two-sided $\alpha = 0.2$ significance level using a Cochrane-Mantel-Haenzel (CMH) test, assuming the same CRR proportions across the strata.

No adjustment will be made for dropouts. Patients withdrawing early from the study or meeting the criteria for treatment failure (including rescue therapy) will not receive any additional study drug, but should be monitored for safety for at least 52 weeks after their last dose of study drug, unless they have withdrawn consent. Patients with missing or incomplete data where a status cannot be determined after applying relevant imputation rules (as defined in Section 4.6), will be set to non-responders.

2.4 ANALYSIS TIMING

The primary analysis will be conducted when all patients have completed the Week 52 study visit or have withdrawn early from the study. The reporting event for the primary analysis will include data for all patients up to their Week 52 assessment date, or data up to the point of withdrawal. BCFU data will not be included within the data-cut. All data will be thoroughly cleaned and will form part of a primary Week 52 Clinical Study Report (CSR) in preparation for a regulatory submission.

A second reporting event will occur after all patients complete the Week 104 visit or withdraw early from the study. A final reporting event and study database lock will occur after all patients complete the treatment and (if applicable) BCFU period or withdraw early from BCFU. Details of these subsequent reporting events will be documented in a separate SAP or specification document.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

After completing the informed consent form, eligible patients will be enrolled into the study and randomized using a central Interactive Voice/Web Response System (IxRS). Patients will be randomly allocated to receive obinutuzumab or placebo in a 1:1 ratio. Randomization will be performed according to a stratified permuted block design — using fixed blocks of size 8 — stratified by race and geographical region.

3.2 DATA MONITORING

Safety data and data pertaining to trial conduct will be reviewed by an independent Data Monitoring Committee (iDMC).

In accordance with the study protocol, the iDMC will meet on a regular basis for formal safety data reviews. The first meeting will occur approximately three months after the first study drug infusion in the first enrolled patient. The iDMC will then meet formally, approximately every three to six months, to review current safety data.

In addition to the regularly scheduled safety reviews, an unscheduled review of the data may be performed at the request of the iDMC or study team, on the basis of a perceived concern for patient safety.

The iDMC will review the results of a planned futility analysis based on the expected pharmacodynamic (PD) effects of obinutuzumab (i.e., $CD19^+$ B-cell depletion as measured by a high sensitivity flow cytometry assay), which is scheduled to be undertaken after 30 subjects have been assigned obinutuzumab and have had their Day 28 $CD19^+$ B-cell count performed.

In addition, an interim efficacy analysis to evaluate CRR will be conducted when the last patient has attended the Week 24 visit. This interim analysis is for Phase III planning purposes only and will have no impact on the progression of this study. The interim analysis will be performed by the independent Data Coordinating Center (iDCC) and interpreted by members of the iDMC.

The Sponsor's study team will have no direct contact with the iDMC during the trial conduct except for the scheduled open sessions of the iDMC.

Further details can be found in the iDMC charter.

4. STATISTICAL METHODS

All analyses, summaries, and listings will be performed using SAS® software (Version 9.4 or later).

4.1 ANALYSIS POPULATIONS

4.1.1 Randomized Population

The randomized population will include all patients randomized into the study.

4.1.2 Pharmacokinetic-Evaluable Population

The pharmacokinetic-evaluable population (PK population) will include all patients randomized to — and received any dose of — obinutuzumab given as study medication, have at least one post-dose pharmacokinetic (PK) sample that is evaluable, and have no major protocol deviations that would impact the PK results.

4.1.3 Safety Population

The safety population will include all randomized patients who received any part of an infusion of study drug. Patients who received the incorrect therapy throughout the study from that assigned at randomization will be reported under the therapy actually received. Patients who were not randomized but who received study drug will be included in the safety population and reported under the therapy actually received.

Patients receiving at least one dose of both active study treatments during the study (e.g., in error, or in the unlikely event of crossing over) will be reported under the original treatment received. Patients who received obinutuzumab as rescue therapy will be reported under the original treatment received before the rescue.

All safety analyses will be performed using the safety population.

4.1.4 Modified Intent-To-Treat Population

The modified intent-to-treat (mITT) population will include all randomized patients who received any part of an infusion of study drug. Patients who received an incorrect therapy will be reported under the treatment arm to which they were randomized.

Patients with no post-baseline data will still be included in the mITT population but will have their efficacy results imputed according to the imputation methods described in Section 4.6.2 for all key efficacy assessments.

Patients who were not randomized but still received study treatment will be excluded from the mITT population.

All efficacy analyses will be performed using the mITT population.

4.1.5 Per Protocol Population

The per protocol (PP) population will include all randomized patients who received any part of an infusion of study drug without significant major protocol deviation. Significant major protocol deviations that will lead to an exclusion in the PP will be decided prior to database lock.

The primary and secondary analyses will be performed using the PP population in addition to the mITT population.

4.2 ANALYSIS OF STUDY CONDUCT

Analyses of study conduct will be carried out on the safety population or all randomized patients, as appropriate.

The patients excluded from each analysis population will be summarized, including the reason for exclusion.

A summary of enrollment by country and investigator site will be produced.

The number of patients who completed or discontinued from the study by Week 52, including the reason for discontinuation, will be summarized by treatment group. A listing of early withdrawals will be produced.

A summary of the number of patients who entered the study and who failed to meet all inclusion/exclusion entry criteria will be produced. Major protocol deviations will be listed.

Patient duration in the 52 week treatment period will be summarized. Duration will be calculated as:

$$\textit{date of last visit} - \textit{date of the first dose} + 1$$

Previous and concomitant medications will be summarised descriptively by mapped term and treatment group. A summary of rescue medications will also be produced.

A summary of the number of patients who experience treatment failure along with the reason(s) for treatment failure will be produced. The number of patients receiving rescue will also be listed and summarised.

A summary of exposure to study treatment will be produced using the dose recorded on the electronic case report form (eCRF). The number of obinutuzumab/placebo infusions and dose received at each infusion and overall will be summarised by treatment group. The total cumulative dose of obinutuzumab/placebo over the 52-week treatment period will be summarised. Note that these summaries highlight adherence to the blinded study treatment and not exposure to the active treatments (which will be described separately). Proportion of patients received rescue medication will be summarized by treatment group.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Summary tables will be produced for the safety population for clinically important baseline demographic and disease characteristics. If it is found that there is a large difference in the number of patients in the safety population compared to the mITT population, additional summaries will be produced based on treatment as randomized.

Demographic and baseline disease characteristics will be summarized as described in the following sections.

4.3.1 Demographics

Demographics will be summarized, including:

- Sex
- Age (years)
- Height (cm)
- Weight (kg)
- Body mass index (kg/m^2)
- Race
- Ethnicity
- Region
- Smoking status
- Female reproductive status

4.3.2 Disease Characteristics

Baseline values will be summarized, including:

- Duration of LN (months)
- Duration of systemic lupus erythematous (SLE) (months)
- Estimated glomerular filtration rate (eGFR) calculated using the CKD-epi formula
- Urine red blood cells (RBCs), white blood cells (WBCs) and RBC casts
- Serum creatinine
- Urinary Protein to Creatinine Ratio
  - 24-hour urine sample and from random sample
  - Proportion of patients with UPCR ≥ 3
  - Time from most recent renal biopsy
- LN biopsy class:
  - Proportion of patients with Class III
  - Proportion of patients with Class IV

  - Proportion of patients with concomitant Class V
  - NIH activity and chronicity scores
- SLEDAI-2K
- Autoantibody positivity:
  - Proportion ANA+
  - Proportion antidsDNA^{+}
  - Proportion anti-Sm^{+}
- Mean C3, C4, and CH50
  - Proportion of low C3, C4, and CH50

Medical history data, including surgery and procedures, MMF/mycophenolic acid (MPA) (including dose) and cyclophosphamide use, and baseline conditions will be summarized descriptively by treatment group using the safety population. A glossary showing the mapping of investigator verbatim terms to diseases will be produced for the medical history data.

4.4 DATA-CUT FOR ANALYSES

For each patient, the day of first dose of study treatment will be designated study Day 1. Each subsequent assessment point will be assigned a study day calculated as:

$$\textit{date of assessment} - \textit{date of first dose} + 1.$$

Data beyond the Week 52 visit or early withdrawal will not be included in the Week 52 CSR. For each patient, data will be cut-off and reported up to and including the exposure date. The exposure date is defined as the earliest of the following:

- Week 52 visit (using upper visit window of Day 364+up to 60 days)
- Date of early withdrawal

Patients who complete the 52-week treatment period but have a missing Week 52 visit, or where the Week 52 visit falls outside the reporting cut-off will be evaluated up to study Day 365 for all analyses involving a duration or exposure element. In such analyses, any references to Week 52 throughout this SAP will imply study Day 365 for these patients.

Although BCFU data will not be included in data displays for the Week 52 primary reporting event, any significant known safety signals or deaths at the time of the data-cut, occurring in BCFU will be highlighted in the CSR.

4.5 VISIT WINDOWS

In general, data for assessments that are collected by scheduled visits will be mapped to visits that appear in the schedule of assessments (Appendix 2) per the protocol using the actual study day of assessment. Data mapped to scheduled visits will include all

data collected up to the reporting cut-off date, and may include withdrawal visits and unscheduled visits. Data will never be mapped to visits for which the assessment was not scheduled in the protocol (i.e., results for an assessment conducted at an unscheduled visit will be mapped to the appropriate visit at which the assessment was scheduled). Visit windows will be continuous from the midpoint between two consecutive study visits, and will be dependent on the schedule of assessments for each variable independently. An example of the Physician's Global Assessment visit window is given in Table 1. Visit windows for each variable will be constructed in the same manner.

Table 1 Time Windows of Study Days to Assign Study Visit for Physician's Global Assessment

Study Visit	Scheduled Study Day	Actual Study Day Time Window
Baseline	1	≤ 1
Week 4	28	$2 \leq \text{day} < 57$
Week 12	84	$57 \leq \text{day} < 127$
Week 24	168	$127 \leq \text{day} < 211$
Week 36	252	$211 \leq \text{day} < 309$
Week 52	364	$309 \leq \text{day}\ 424$

Derived variables that are collected on an ongoing basis will be presented using appropriate time intervals.

Data displays that are presented by visit will only include visits at which the assessment was scheduled to be collected. The methods for handling multiple values within a visit window are described in Section 4.9.3.

4.6 EFFICACY ANALYSIS

The primary and secondary efficacy analyses will include all randomized patients who received any study medication, with patients grouped according to the treatment assigned at randomization.

The primary and secondary endpoints will be tested at an overall 20% significance level using two-sided hypothesis tests.

To control for overall Type I error, the hypothesis testing on study endpoints will be conducted sequentially starting with the primary endpoint at 20% level of significance. If the null hypothesis relating to the primary endpoint is rejected, the secondary endpoints will then be tested in a hierarchical fashion in the following sequence, each at 20% level of significance:

1. Proportional analysis of patients who achieve an overall response at Week 52 (CRR+PRR)
2. Proportion of patients that achieve a modified CRR (mCRR1) at Week 52 employing the primary−efficacy measure definition and removing the urinary sediment analysis criteria
3. Proportion of patients that achieve a second modified CRR (mCRR2) at Week 52
4. Decrease in anti-dsDNA titers
5. Increase in C3 levels
6. Increase in C4 levels
7. Time to overall response (CRR+PRR) over the course of 52 weeks
8. Proportion of patients that achieve a PRR at Week 52
9. Time to CRR, over the course of 52 weeks
10. Proportion of patients that achieve a third modified CRR (mCRR3) at Week 52
11. Proportion of patients who achieve a CRR at Week 24

If at any step in the testing procedure, the p-value associated with a test is not <0.20, the remaining endpoints below the sequence will not be considered statistically significant.

4.6.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients achieving CRR at Week 52.

The following two-sided hypothesis will be tested at the 20% significance level (double-sided):

$$H_0: \rho_{MMF+OBZ} - \rho_{MMF+PBO} = \pm 20\ \%$$

$$H_1: \rho_{MMF+OBZ} - \rho_{MMF+PBO} \neq \pm 20\ \%$$

where ρ denotes the proportion of patients achieving complete renal response; PBO=Placebo; and OBZ=Obinutuzumab.

The primary method for comparing the proportion of patients achieving sustained complete remission will be the Cochran-Mantel-Haenszel test. The analysis will be stratified by the stratification factors applied at randomization. The proportion of patients

achieving sustained complete remission in each treatment group will be presented along with the adjusted difference, 95% confidence interval for the difference, and p-value.

4.6.1.1 Complete Renal Response at Week 52

A patient will be considered a responder for complete renal response if the following conditions are met at the Week 52 visit:

- Normalization of serum creatinine as evidenced by the following:
  - Serum creatinine $\leq$ the upper limit of normal (ULN) range of central laboratory values if baseline (Day 1) serum creatinine is above the ULN
  - Serum creatinine $\leq$ 15% above baseline and $\leq$ the ULN range of central laboratory values if baseline (Day 1) serum creatinine is $\leq$ the ULN range of *central laboratory values
- Inactive urinary sediment as evidenced by:
  - $<$10 RBCs/high-power field (HPF);and
  - the absence of red cell casts
- Urinary protein to creatinine ratio $<$0.5

Any patient who switches to rescue medication prior to Week 52 will be considered a non-responder.

Patients who withdraw prior to Week 52 from the study or meet the criteria for treatment failure will be evaluated using data up to the point of withdrawal or treatment failure only, whichever occurs first. They will be deemed non-responders.

Complete renal response is a composite endpoint derived using several sources of information. Methods for data handling and dealing with missing data for the components of the primary endpoint are provided below. Any missing or ambiguous data will be queried and all efforts will be made to resolve data issues prior to database lock.

If any of the conditions for complete renal response are still missing after the below imputation rules are applied, then the patient will be set to non-responder.

4.6.1.2 Serum Creatinine

Only creatinine data obtained from the central laboratory will be used for efficacy analysis.

Missing Data: If Day 1 serum creatinine data is missing, then the screening value will be imputed. Missing serum creatinine at Week 52 will be imputed using the value from Week 36. If still missing then, no imputation will be made.

4.6.1.3 Inactive Urinary Sediment

Urine sediment data from the local laboratory will be prioritized in the efficacy analysis given the time-sensitive nature of this analysis and the delay between local specimen collection and central laboratory analysis. The central laboratory data will be used when local laboratory data are missing using the strategy highlighted below.

Missing Data

If Day 1 urine sediment data from local lab is missing, then the Day 1 central lab value will be used. If both central and local lab values are missing at Day 1, then screening value from the local lab will be used for imputation, followed by the screening central lab value.

Missing counts of RBC from local laboratory at Week 52 will be imputed using the value from the central laboratory at Week 52 first; if still missing then impute the value from Week 36 local laboratory first, and if still missing then impute the value from Week 36 central laboratory. If the value is still missing then no imputation will be made.

Missing counts of RBC casts from local laboratory at Week 52 will be imputed using the value from the central laboratory at Week 52 first; if still missing then the value from Week 36 local laboratory will be imputed first, and if still missing the value from Week 36 central laboratory will be imputed. If the value is still missing, then “casts absent” will be imputed.

4.6.1.3.1 Urinary Protein to Creatinine Ratio

Only Urinary Protein to Creatinine Ratio (UPCR) (mg/mg) data obtained from the central laboratory will be used for efficacy analysis with the exception of the first 4 patients enrolled into the study. Through a laboratory error, baseline UPCR was not calculated for these subjects. In this case, local values for UPCR will be used, if available.

Missing Data

Missing 24-hour UPCR at Day 1 will be imputed in the following order:

- 24-hour UPCR from the screening visit (central laboratory)
- Spot UPCR from the Day 1 visit (central laboratory)
- Spot UPCR from the screening visit (central laboratory)

Missing 24-hour UPCR at Week 52 will be imputed in the following order:

- Spot UPCR from the Week 52 visit (central laboratory)
- 24-hour UPCR from Week 36 visit (central laboratory)
- Spot UPCR from Week 36 visit (central laboratory)

4.6.1.4 Treatment Failure

Treatment failure occurs in the following scenarios:

- Patients who do not exhibit a response to the initial 2-week course of increased corticosteroids for treatment of renal flares and who initiate a new immunosuppressive therapy.
- If patients require a new immunosuppressive drug (other than corticosteroids) for treatment of their extrarenal SLE flare, those patients will be counted as treatment failures and will not receive further study drug but will continue their protocol mandated study visits.
- Any patient who switches to rescue medication prior to Week 52 will be considered a non-responder.

The clinical definitions of treatment failure above are aligned with "non-responder" classification for the primary analysis. Patients experiencing treatment failure prior to achieving complete renal response at Week 52 will be categorized as non-responders in the primary analysis but will continue to be followed in the study per the schedule of assessments. Patients who achieve complete renal response at Week 52 without experiencing an event constituting treatment failure beforehand will not be categorized as non-responders, regardless of whether they subsequently meet the criteria.

Patients who experience treatment failure are eligible to receive rescue therapy during the treatment period as per the investigator's best medical judgment. Patients who receive rescue therapy will continue to be followed in the study per the schedule of assessments.

Patients who receive rescue therapy for LN will be evaluated up to the point of rescue only for all main efficacy analyses. Methods for data handling and/or imputing post-rescue data are described throughout Section 4.6.1. Additional exploratory summaries on key efficacy assessments will be produced that will include rescue data. Safety analyses will include data up to the point of rescue only.

Listings will be provided for all data, including rescue data.

Depending on the proportion of patients receiving rescue, patients will be analyzed separately using descriptive statistics for key analyses on study conduct, efficacy, and safety. For relevant summaries, patients may be re-baselined at the time of rescue and data presented as pre- and post-rescue treatment. Rescue analyses will use data as observed.

Subject to patient counts, a limited number of analyses may be summarized by type of rescue received.

4.6.1.5 Sensitivity Analyses

A sensitivity analysis of the primary endpoint data will be conducted excluding 62 patients whose treatment arm information were potentially unblinded at 24 sites during the course of the study. This issue has been documented in a corrective action and preventive action (CAPA) dated 21 December 2017. While there were reasons to believe that unblinding did not occur, this sensitivity analysis will assess the robustness of efficacy results if affected patients are excluded from the dataset. See Section 4.6.2.4 for additional sensitivity analyses using modified definitions of the primary endpoint.

4.6.2 Secondary Efficacy Endpoints

4.6.2.1 Overall Renal Response

The proportion of patients who achieve an overall response at Week 52 (CRR+PRR) will be analyzed using a CMH test, with race and region as strata.

The proportion of patients achieving PRR at Week 52 as defined by achievement of all of the following:

- Serum creatinine ≤15% above baseline value
- No urinary red cell casts and either RBCs/HPF ≤ 50% above baseline or < 10 RBCs/HPF
- 50% improvement in the urine protein to creatinine ratio, with one of the following conditions met:
  - If the baseline urine protein to creatinine ratio is ≤3.0, then a urine protein to creatinine ratio of <1.0
  - If the baseline protein to creatinine ratio is >3.0, then a urine protein to creatinine ratio of <3.0

Missing Data

Missing data for each component of the endpoint at baseline and at Week 52 will be imputed using the relevant approach discussed in Section 4.6.1.

Time to First Overall Response

Time to first overall response (CRR+PRR) over the course of 52 weeks will be presented using Kaplan-Meier methodology and compared between treatment groups using a stratified log-rank test with race and region as strata. Time to CRR during this period will be analyzed similarly.

4.6.2.2 Biomarkers of Lupus Nephritis

The percent change from baseline and absolute value of biomarkers of LN disease activity will be summarized by treatment arm using tables and graphs. These biomarkers may include changes in anti-dsDNA antibody levels and in C3, C4, and CH50 levels.

Missing Data

Missing data at Week 52 will be imputed using last observation carried forward (LOCF).

4.6.2.3 Complete Renal Response at Week 24

The proportions of patients who achieve a CRR at Week 24 will be analyzed using similar methodology as the primary analysis.

Missing Data for Serum Creatinine at Week 24

Missing serum creatinine at Week 24 will be imputed using the value from Week 12 first, and if still missing, then take the value from Week 26. If still missing then, no imputation will be made.

Missing Data for Inactive Urinary Sediment at Week 24

Missing counts of RBC from local laboratory at Week 24 will be imputed using the value from the central laboratory at Week 24 first; if still missing then impute the value from Week 12 local laboratory first, and if still missing, then impute the value from Week 12 central laboratory. If the value is still missing then no imputation will be made.

Missing Data for UPCR (24-Hour) at Week 24

Missing 24-hour UPCR at Week 24 will be imputed in the following order:

- Spot UPCR from the Week 24 visit (central laboratory)
- 24-hour UPCR from Week 12 visit (central laboratory)
- Spot UPCR from Week 12 visit (central laboratory)

4.6.2.4 Modified Complete Renal Response

In addition, the modified definitions, mCRR1, mCRR2, and mCRR3 of CRR will be analyzed to assess the sensitivity of CRR to its definition.

- Proportion of patients who achieve a modified CRR (mCRR1) at Week 52 employing the primary−efficacy measure definition and removing the urinary sediment analysis criteria.

  mCRR1 is defined by attainment of normalization of serum creatinine as evidenced by the following:

  - Serum creatinine $\leq$ the ULN range of central laboratory values if baseline (Day 1) serum creatinine is above the ULN
  - Serum creatinine $\leq$15% above baseline and $\leq$ the ULN range of central laboratory values if baseline (Day 1) serum creatinine $\leq$the ULN range of central laboratory values
  - Urinary protein to creatinine ratio $<$0.5
- Proportion of patients that achieve a second modified CRR (mCRR2) at Week 52 as defined by attainment of the following:
  - Serum creatinine $\leq$ 15% above baseline if baseline (Day 1) serum creatinine is above the normal range of the central laboratory values

  - Serum creatinine ≤ the ULN range of central laboratory values if baseline (Day 1) serum creatinine is ≤ the ULN range of central laboratory values
  - Inactive urinary sediment (as evidenced by < 10 RBCs/HPF and the absence of red cell casts)
  - Urinary protein to creatinine ratio < 0.5
- Proportion of patients that achieve a third modified CRR (mCRR3) at Week 52 as defined by attainment of the following:
  - Serum creatinine ≤ the ULN range of central laboratory values
  - Urinary protein to creatinine ratio < 0.5

Missing Data

Missing data for each component of the endpoint at baseline and at Week 52 will be imputed using the relevant approach discussed in Section 4.6.1.1.

4.6.3 Exploratory Efficacy Endpoints

The following endpoints will provide additional information to assess treatment efficacy during the 52-week double blind treatment period.

4.6.3.1 Response Endpoints

Proportion of patients achieving CRR, mCRR1, mCRR2, or mCRR3 at additional timepoints, including Week 12 and Week 36. These will be summarized using frequency counts and percentages. Graphical displays will be used where relevant to show trends over time. Missing data imputation will be similar to the approach taken in Section 4.6.2.3 for the Week 24 efficacy analysis.

4.6.3.2 B Cells

Change in B cells and subsets over the course of the study. Summary statistics will be used to summarize the data and graphical displays will be used to show the trends over time.

4.6.3.3 Biomarkers

Change in serum and urine biomarkers over the course of the study. Summary statistics will be used to summarize the data and graphical displays will be used to show the trends over time.

4.6.3.4 Extra renal Flares

Proportion of patients experiencing an extra renal flare over 52 weeks. This will be summarized using frequency counts and percentages. Graphical displays will be used where to show trends over time.

4.6.3.5 Renal Flares

Proportion of patients experiencing a renal flare over 52 weeks and 104 weeks. This will be summarized using frequency counts and percentages. Graphical displays will be used where to show trends over time.

4.6.3.6 Physician's Global Assessment

Change in Physician's Global Assessment over 52 weeks. Summary statistics will be used to describe the data and graphical displays will be used to show the trends over time.

4.6.3.7 Glucocorticoid Toxicity Change Index

Change in Glucocorticoid Toxicity Change Index (GTCI) and individual GTCI domains over 52 weeks. Summary statistics will be used to summarize the data and graphical displays will be used to show the trends over time.

4.6.3.8 Renal Biopsy Histopathology

Change in renal biopsy histopathology over time. Summary statistics will be used to summarize the data and graphical displays will be used to show the trends over time.

4.7 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Pharmacokinetic (PK) parameters will be determined for all patients with serum concentration data by the method that best describes the data. This may be non-compartmental analysis, compartmental analysis for each individual patient, or population PK analysis. PK parameters will be computed for all patients with serum concentration data except for patients who are noncompliant to dosing and/or sampling schedule or whose samples have interference by ADAs (anti-drug antibodies) (which precludes data inclusion); these patients will be excluded from the analysis.

PK analysis will include an exploratory analysis to identify baseline covariates that affect the pharmacokinetics of obinutuzumab in this patient population. Baseline covariates that will be examined include demographics, other patient characteristics (such as disease severity), and selected laboratory measures. The primary pharmacodynamic (PD) marker will be $CD19^{+}$ B-cell counts. Exploratory PD markers from blood samples will be summarized graphically and descriptively over time by treatment arm; these markers include B-cell subsets serum BAFF, and quantitative Ig levels (total, IgG, IgM, and IgA).

In addition, the percent change from baseline for each marker will be computed at each sampling timepoint using the Day 1 pre-dose value as the baseline point.

Exploratory analyses will be performed to assess the possible relationship between obinutuzumab dosing, PD markers, PK measures, and clinical response.

4.8 SAFETY ANALYSES

The safety analysis will be performed on the safety population as defined in Section 4.1.3. Analyses of safety data will include rescue patients up to the point of rescue only. Rescue patients will be summarized separately for key safety outputs.

4.8.1 Exposure to Study Medication

The number and percentage of patients who received obinutuzumab will be summarized by treatment course, along with summary statistics for the dose of obinutuzumab received at each infusion and overall, and the duration of exposure. Duration of exposure will be calculated as:

exposure date (as defined in Section 4.4) − date of first infusion + 1.

Obinutuzumab exposure data will be determined using the dosing information as recorded on the obinutuzumab administration log on the eCRF and the actual treatment received as per IxRS. Exposure to obinutuzumab will not include obinutuzumab given as rescue, which will be analyzed separately.

Exposure to MMF will be summarized using the average daily dose, total cumulative dose, and treatment duration. Treatment duration will be calculated as:

date of last dose − date of first dose + 1

The total cumulative dose will be calculated by summing the total daily dose over the treatment duration. Average daily dose will be calculated as:

total cumulative dose ÷ treatment duration

MMF exposure data will be determined using the dosing information as recorded on the MMF administration log on the eCRF and the actual treatment received as per IxRS. Exposure to MMF will not include MMF given as rescue, which will be analyzed separately.

Exposure to corticosteroids (CS) will be summarized using the average daily dose, total cumulative dose, and treatment duration. Treatment duration will be calculated as:

date of last dose − date of first dose + 1

The total cumulative dose will be calculated by summing the total daily dose over the treatment duration. Average daily dose will be calculated as:

total cumulative dose ÷ treatment duration

CS exposure data will be determined using the dosing information as recorded on the conmed administration log on the eCRF and the actual treatment received as per IxRS. Exposure to CS will not include CS given as rescue, which will be analyzed separately.

Cumulative CS exposure will be summarized in two ways: (1) cumulative CS exposure from study Day 1; (2) Cumulative CS exposure from the Screening Visit.

4.8.2 Adverse Events

Adverse events will be mapped and reported using the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus using the most current version at the time of analysis (Version 20.1 or later). Glossaries showing the mapping of investigator verbatim terms to coded events will be produced.

A listing of SAEs occurring during screening will be produced.

Treatment-emergent adverse events (TEAEs) will be summarized. All AEs referenced in the section below will be TEAEs. TEAEs are defined as those AEs with observed or imputed onset date on or after the start date of trial treatment. Only where the most extreme intensity is greater than the initial intensity (or if most extreme intensity is not missing and initial intensity is missing) will events with an onset date prior to the start of trial treatment be considered treatment-emergent. An AE with a completely missing start date will be assumed to be treatment-emergent unless the AE has a complete non-imputed end date that is prior to study Day 1.

Listings will show all AEs reported, including AEs occurring after rescue therapy, and any AEs that may have occurred during the oral corticosteroid dose adjustments in the screening period.

AEs will be summarized by system organ class (SOC) and preferred term (PT), and will be presented in order of descending frequency summed across the treatment arms within each SOC and PT.

The following will be summarized, and/or listings produced where required:

- All AEs
- Serious Adverse Events (SAEs)
- AEs by relationship to obinutuzumab/placebo
- AEs by relationship to MMF/MPA
- Corticosteroid-related adverse events
- AEs leading to study drug dose modification or interruption
- AEs by common terminology criteria grade
- Infections
- Serious Infections
- Infusion related reactions (IRRs)
- Serious IRRs
- AEs leading to withdrawal
- AEs leading to death

AEs to monitor will be listed, including:

- Opportunistic infections (Roche Standard AE Grouped Term [AEGT] Basket)

If an imbalance in exposure is found between treatment groups, AE rates per 100 patient-years exposure may be calculated. AE rate per 100 patient-years is defined as:

$$(\text{number of events} \div \text{total exposure}) \times 100$$

The 95% CIs will be calculated based on exact Chi-Squared (X^2) distribution.

Positive pregnancy results will be listed, as identified using the serum test results.

4.8.3 Deaths

Details of any deaths will be presented in the form of an individual patient listing.

4.8.4 Laboratory Data

4.8.4.1 Safety Laboratory Parameters

All laboratory data will be converted to SI units. The International Standard for the Handling and Reporting of Laboratory Data COG 3007 will be used to implement reference ranges and marked abnormalities for laboratory data where possible. Additionally, serum creatinine, hemoglobin, and hematocrit will be presented in conventional units.

Summary statistics for the absolute and change from baseline values will be produced by visit for laboratory parameters.

Marked abnormalities will be summarized for laboratory parameters. Summaries by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade will also be produced for certain lab assessments, including shift tables from baseline to highest grade post-baseline.

Shift tables from baseline to highest NCI CTCAE grade post-baseline will be produced for liver function laboratory tests.

4.8.4.2 Immunoglobulins

The absolute values and change from baseline will be summarized by treatment group and visit for total Ig, IgA, IgG, and IgM.

The proportion of patients with a value of total Ig, IgA, IgG, and IgM which is less than the lower of limit of normal per visit will be produced.

A plot of the mean value over time will be produced for total Ig, IgA, IgG, and IgM. The plots will display error bars (mean$\pm$standard deviation) around the mean.

4.8.4.3 Lymphocyte Populations

The following lymphocyte subsets will be analyzed:

- **TBNK analytes:**
  - $CD19^+$ B cells per microliter
  - $CD3^+$ T cells per microliter
  - $CD3^+CD8^+$ T_C cells per microliter
  - $CD3^+CD4^+$ T_H cells per microliter
  - $CD16^+CD56^+$ NK cells per microliter
- **HSFC (MRB 1.1 and BCP 2.2) analytes:**
  - $CD19^+$ B cells per microliter
  - $CD19^+$ $CD27^+$ memory B cells per microliter
  - $CD19^+$ CD27neg IgD^+ naïve B cells per microliter
  - $CD19^+CD27^+$CD38high plasmablasts/plasma cells per microliter

The absolute and change from baseline values will be summarized by visit and treatment group for all lymphocytes.

The proportion of patients with a lymphocyte value less than the lower limit of normal by visit and treatment group will be produced for the following lymphocytes measured via TBNK:

- CD3
- CD4
- CD8
- CD19

A plot of the mean values over the 52-week treatment period will be produced for the following, by visit and treatment group:

- **TBNK analytes:**
  - $CD19^+$ B cells per microliter
  - $CD3^+$ T cells per microliter
  - $CD3^+CD8^+$ TC cells per microliter
  - $CD3^+CD4^+$ TH cells per microliter
  - $CD16^+CD56^+$ NK cells per microliter
- **HSFC (MRB 1.1 and BCP 2.2) analytes:**
  - $CD19^+$ B cells per microliter
  - $CD19^+$ $CD27^+$ memory B cells per microliter
  - $CD19^+$ CD27neg IgD^+ naïve B cells per microliter

- $CD19^{+}CD27^{+}CD38high$ plasmablasts/plasma cells per microliter

Plots will display error bars (mean $\pm$ standard deviation) around the mean.

4.8.5 Vital Signs

Vital signs are measured at each scheduled visit in accordance with the schedule of assessments (see protocol); Baseline, Week 2, Week 4, Week 12, Week 24, Week 26, Week 36, and Week 52. At infusion visits, vital signs should be taken pre-infusion, then every 15 minutes for 1 hour, then every 30 minutes until the end of the infusion, and within 30 minutes post-infusion. Additional readings may be obtained at the discretion of the investigator in the event of an infusion-related reaction.

Summary tables for the absolute value and change from baseline in vital sign assessments will be presented by visit up to Week 52. Vital sign assessments include respiratory rate, pulse rate, temperature, systolic and diastolic blood pressure. Body weight will be measured at baseline, Week 24, and Week 52. Body mass index will be calculated for these time points.

4.9 DATA HANDLING METHODS

4.9.1 Presentation of Data

Data displays include listings, tables, and plots. All data displays will be presented by treatment group.

Data presented in summary tables will be displayed using summary statistics. Continuous data will include number of patients, mean, standard deviation, median, minimum, and maximum. Categorical data will include the number and percentage of patients.

Summary tables for CRR at Week 52 will have in the following variables as stratification:

Race, region, baseline UPCR ≥ 3 versus <3, B-cell depleters versus non-depleters, serum creatinine $\leq$ ULN versus $>$ULN, and by baseline biopsy histology (Class III vs. Class IV, and concomitant Class V vs. no Class V)

4.9.2 Definitions

Baseline

Baseline is defined as the last non-missing value prior to receipt of study treatment. Typically, baseline will be the pre-dose Day 1 assessment, but may include screening results if the pre-dose Day 1 result is not available or missing. If the Day 1 or screening result is missing then no imputation will be made and the baseline result will be set to missing.

Study Day

For each patient, the first day of study treatment will be designated study Day 1. Each subsequent assessment will be assigned a study day calculated as:

$$date\ of\ assessment - date\ of\ first\ dose + 1$$

4.9.3 Multiple Values

For summaries displayed by visit, multiple values for a given assessment within a time window will be handled as follows:

Efficacy

The nearest non-missing assessment to the nominal timepoint will be assigned to the visit. If two or more values are equidistant from the nominal timepoint, then the latest assessment will be selected.

Safety

The assessment with the worst result will be assigned to the visit.

4.9.4 Missing Data

Methods for handling missing data for efficacy analyses are described in detail throughout Section 4.6.1. Missing or partial dates for AEs, concomitant medications (except oral corticosteroids), laboratory assessments, and medical history will be imputed as detailed in Appendix 3.

4.10 INTERIM ANALYSES

Pharmacodynamic Futility Interim Analysis

An interim analysis for futility is planned on the basis of CD19 B-cell counts after 30 patients have been assigned to the obinutuzumab arm and have had their Day 28 blood $CD19^+$ B-cell counts assessed by HSFC. The effect of rituximab on $CD19^+$ B-cell counts has been measured by HSFC in an investigator sponsored study in which peripheral B-cell depletion below the lower limit of quantification (LLOQ) of the assay occurred in 46% of patients. Slightly less than half of these rituximab treated patients with full peripheral B-cell depletion achieved a major clinical response, with the remainder of the patients having partial clinical responses. Therefore, it is hypothesized that an improved outcome over rituximab is achievable for a LN patient population with full peripheral B-cell depletion, with the assumption that improved tissue depletion with treatment will parallel the peripheral depletion. To test the hypothesis in this study, we will require at least 50% of the obinutuzumab-treated patients to have peripheral B-cell depletion below the LLOQ of the HSFC assay in order to have a realistic chance of a positive primary endpoint analysis for the treatment arm. Quantification of the link between this biomarker and the study's primary analysis has not been established; therefore predictive probabilities for study statistical significance cannot be provided. Consequently, the study will be terminated if the 5% one-sided Clopper-Pearson upper confidence limit for the proportion of patients who achieve B-cell depletion is not greater than 0.5. Assuming that there are 30 patients at the time of the interim analysis, this will

effectively require that ≥11 obinutuzumab patients have complete B-cell depletion below the LLOQ of the HSFC assay at the time of the interim analysis.

The interim analysis will be performed by the iDMC, which may recommend that the study be stopped for futility if the futility criterion is satisfied. Additional criteria for recommending that the study be stopped for futility may be added to the iDMC Charter. As this interim analysis will only result in termination of the study due to futility and not for efficacy, an adjustment to the α–level is not required. Although the outcome of the interim analysis may reduce the power of this study to below the estimated 83%, a sample size adjustment has not been made.

Renal Response Interim Analysis

The iDMC will also conduct an interim efficacy analysis to evaluate renal response when the last patient has achieved the 6-month visit. The interim analysis will be performed by the iDCC and interpreted by members of the iDMC. The iDMC may recommend to the Sponsor to consider the planning of Phase III if the treatment difference (obinutuzumab minus placebo) in complete renal response at Week 24 is ≥10%. In addition, the iDMC will inform the Sponsor if the treatment difference (obinutuzumab minus placebo) in complete renal response at Week 24 is ≥20%.

5. REFERENCES

Not applicable.

Appendix 1
Protocol Synopsis

TITLE:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF OBINUTUZUMAB IN PATIENTS WITH ISN/RPS 2003 CLASS III OR IV LUPUS NEPHRITIS**
PROTOCOL NUMBER:	WA29748
VERSION NUMBER:	3
EUDRACT NUMBER:	2015-002022-39
IND NUMBER:	125,054
TEST PRODUCT:	Obinutuzumab (GA101; RO5072759)
INDICATION:	ISN/RPS Class III or IV Lupus Nephritis
SPONSOR:	F. Hoffmann-La Roche Ltd.

Objectives

Efficacy Objectives

The primary efficacy objective for this study is as follows:

1. To evaluate the efficacy of obinutuzumab compared with placebo in patients with International Society of Nephrology (ISN)/Renal Pathology Society (RPS) Class III or IV lupus nephritis (LN) as measured by complete renal response (CRR) at 52 weeks

The secondary efficacy objectives for this study are as follows:

- To assess overall renal response (defined as CRR plus partial renal response [PRR])
- To evaluate the ability of obinutuzumab to improve time-to-response (CRR plus PRR) over the course of 52 weeks

Safety Objectives

The safety objectives for this study are as follows:

2. To evaluate the safety of obinutuzumab compared with placebo in patients with Class III or IV LN, focusing on the nature, frequency, and severity of serious and non-serious adverse events, as well as effects on laboratory values, vital signs, or other safety biomarkers
3. To characterize the immunogenic potential of obinutuzumab by measuring human anti-drug antibodies and assessing their relationship with other outcome measures
4. To fully characterize adverse events of special interest, including infusion reactions, infections, thrombocytopenia, and neutropenia

Pharmacodynamic Objective

The pharmacodynamic (PD) objective for this study is as follows:

5. To compare changes in CD19+ B cells in the peripheral blood following treatment with obinutuzumab versus placebo

Pharmacokinetic Objectives

The pharmacokinetic (PK) objectives for this study are as follows:

- To characterize the pharmacokinetics of obinutuzumab in the LN population
- To assess potential PK interactions between obinutuzumab and concomitant medications, including mycophenolate mofetil (MMF)

Patient-Reported Outcome Objectives

The patient-reported outcome (PRO) objective for this study is as follows:

- To assess the change from baseline of the patient's general health over the course of the study by use of the Subject's Global Assessment

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To evaluate pre-dose levels of exploratory biomarkers (which may include but are not limited to B-cell subsets and levels of protein and mRNA in serum, *plasma,* blood, and urine) and potential associations with outcome
- To evaluate changes in exploratory biomarkers (which may include but are not limited to B-cell subsets and levels of protein and mRNA in serum, *plasma,* blood, and urine) over time in patients dosed with obinutuzumab versus patients dosed with placebo
- To evaluate the occurrence of extrarenal flares
- To evaluate the impact of therapy on patient and physician-reported outcomes
- *To assess damage through the Glucocorticoid Toxicity Change Index (GTCI)*
- To assess renal biopsy histopathology (for the presence and depletion of B cells at the screening biopsy and from subsequent biopsies)

Additional exploratory objectives and outcome measures will be included in a final Statistical Analysis Plan (SAP).

Study Design

Description of Study

This Phase II study is a parallel-group, double-blind, randomized, placebo-controlled study comparing the efficacy and safety of obinutuzumab plus MMF with placebo plus MMF in Class III and IV patients with proliferative LN. The Sponsor intends to enroll approximately 120 patients diagnosed with ISN/RPS Class III or IV LN, with a diagnosis of systemic lupus erythematosus (SLE) based on current American College of Rheumatology (ACR) criteria (at least 4 criteria must be present, one of which must be a positive anti-nuclear antibody [ANA]), in centers throughout the world. In addition to study treatment, patients will receive standard-of-care therapy with angiotensin-converting enzyme (ACE) inhibitors/angiotensin-II–receptor blockers, MMF (dosed at 2.0–2.5 g/day) *or mycophenolic acid (MPA) (dosed 1440–1800 mg/day)*, and a prednisone taper. Patients must be 18–75 years of age and have ISN/RPS 2003 Class III or IV proliferative LN as evidenced by renal biopsy performed within 6 months prior to *or during screening* and may have concomitant Class V disease (e.g., Class III/V or Class IV/V). Patients with Class III (C) or Class IV (C) disease will be excluded because of the lower likelihood of response within these categories. Patients must exhibit significant proteinuria (urine protein to creatinine ratio > 1.0 *based on a 24-hour urine collection)*. Key exclusions will be evidence of severe renal impairment (estimated glomerular filtration rate [GFR] *< 30 mL*/minute per 1.73 m_2 of body surface area), end-stage renal disease requiring dialysis or transplantation, evidence of active infections, and other safety-related exclusions. Patients will receive an initial 1000 mg of methylprednisolone intravenous (IV) prior to or during screening, and may receive up to a total of 3000 mg methylprednisolone IV prior to randomization for severe clinical activity according to guidelines of routine care for these patients. Patients will receive 80 mg methylprednisolone (or methylprednisolone placebo) on the day of the obinutuzumab/placebo infusion to reduce infusion-related reactions. *Oral corticosteroids* will be *initiated at a dose of* 0.5 mg/kg *(maximum 60 mg/day)* and will be reduced over *10* weeks. This modified taper, from the LUNAR study, will be initiated at a lower dose in recognition that prednisone doses above 10 mg/day are associated with significant adverse events, including increased risk of cardiovascular events. Prior

experience with rituximab suggests that it can potentially enable complete and PRRs in the absence of oral prednisone or a prednisone taper, thus allowing the use of lower doses of corticosteroids as proposed in this Phase II protocol.

Patients will be followed until *at least Week 104, with* the primary endpoint evaluation *at Week 52. An* interim analysis at 6 months will be performed to evaluate early differences in CRR. All patients will have central reading of the renal biopsy histopathology and will also receive repeat renal biopsy as available on the basis of clinical status and local practice. All patients will be evaluated by high-sensitivity flow cytometry (HSFC) to evaluate the ability of obinutuzumab to deplete circulating peripheral B cells, and an interim PD analysis will be performed to assess whether patients do not fully deplete peripheral CD19 B cells as anticipated. These mechanistic studies and more intensive histopathologic reviews are intended to test the hypothesis that greater B-cell depletion in the target organ (kidney) and associated secondary lymphoid structures will translate into greater CRR rates.

Number of Patients

The study will enroll approximately 120 patients with active ISN/RPS 2003 Class III or IV LN at approximately sixty centers in North America, South America, Europe, and selected other countries.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed Informed Consent Form
2. Age 18−75 years
3. Ability to comply with the study protocol, in the investigator's judgment
4. Diagnosis of SLE, according to current ACR criteria (at least four criteria must be present, one of which must be a positive ANA)
5. Diagnosis of ISN/RPS 2003 Class III or IV LN as evidenced by renal biopsy performed within 6 months prior to *or during* screening. Patients may co-exhibit Class V disease in addition to either Class III or Class IV disease.
6. Proteinuria (urine protein to creatinine ratio) $>$ 1.0, based on a 24-hour urine collection
7. For women who are not postmenopausal ($\geq$ 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use two adequate methods of contraception, including at least one method with a failure rate of $<$ 1% per year, during the treatment period and for at least 18 months after the last dose of study drug

   Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

   Barrier methods must always be supplemented with the use of a spermicide.

   Examples of contraceptive methods with a failure rate of $<$ 1% per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices.
8. For men: agreement to remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<$ 1% per year during the treatment period and for at least 12 months after the last dose of study drug and agreement to refrain from donating sperm during this same period

   Men with a pregnant partner must agree to remain abstinent or use a condom for the duration of the pregnancy.

   Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or

postovulation methods) and withdrawal are not acceptable methods of contraception.

Patients must be willing to practice this method of contraception while taking MMF and for *90 days* after stopping MMF.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

9. Retinitis, poorly controlled seizure disorder, acute confusional state, myelitis, stroke or stroke syndrome, cerebellar ataxia, or dementia that is currently active and resulting from SLE
10. Presence of rapidly progressive glomerulonephritis defined by

    The presence of crescent formation in $\geq 50\%$ of glomeruli assessed on renal biopsy or

    Sustained doubling of serum creatinine within 12 weeks of screening *or*

    The investigator's opinion that the patient has rapidly progressive glomerulonephritis.
11. Severe renal impairment as defined by estimated GFR < 30 mL/min or the need for dialysis or renal transplant
12. Greater than 50% of glomeruli with sclerosis on renal biopsy
13. Treatment with cyclophosphamide or calcineurin inhibitors within the 3 months prior to randomization
14. Unstable disease with thrombocytopenia or at high risk for developing clinically significant bleeding or organ dysfunction requiring therapies such as plasmapheresis or acute blood or platelet transfusions
15. Lack of peripheral venous access
16. Pregnancy or lactation
17. History of severe allergic or anaphylactic reactions to monoclonal antibodies or known hypersensitivity to any component of the obinutuzumab infusion
18. Significant or uncontrolled medical disease in any organ system not related to SLE or LN, which, in the investigator's opinion, would preclude patient participation
19. Concomitant chronic conditions, excluding SLE, (e.g., asthma, Crohn's disease) that required oral or systemic steroid use in the 52 weeks prior to screening
20. Known HIV infection
21. Known active infection of any kind (excluding fungal infection of nail beds) or any major episode of infection requiring hospitalization or treatment with IV anti-infectives within 8 weeks of the screening visit or oral anti-infectives within 2 weeks prior to the screening visit
22. History of serious recurrent or chronic infection
23. History of cancer, including solid tumors, hematological malignancies, and carcinoma in situ (except basal cell carcinomas of the skin that have been treated or excised and have resolved)
24. Currently active alcohol or drug abuse or history of alcohol or drug abuse within 52 weeks prior to screening
25. Major surgery requiring hospitalization within 4 weeks of randomization (excluding diagnostic surgery)
26. Previous treatment with *an anti-CD20*–targeted therapy within 12 months of randomization
27. *Previous treatment with a biologic B-cell–targeted therapy (other than anti-CD20) within 6 months of randomization*
28. Treatment with any investigational agent within 28 days of randomization or five half-lives of the investigational drug (whichever is longer)
29. Receipt of a live vaccine within 28 days prior to screening
30. Intolerance or contraindication to oral or IV corticosteroids
31. Aspartate aminotransferase or alanine aminotransferase $> 2.5 \times$ upper limit of normal (ULN)

32. Amylase or lipase $> 2 \times$ ULN
33. Neutrophils $< 1.5 \times 10^3$/・L
34. Positive hepatitis B surface antigen (HbSAg) or hepatitis C serology. Patients who are HBsAg negative and hepatitis B core antibody positive with no detectable DNA will be allowed into the study but will require regular monitoring of hepatitis B virus DNA.
35. Hemoglobin < 7 g/dL, unless caused by autoimmune hemolytic anemia resulting from SLE
36. Platelet count $< 10{,}000/\mu L$
37. Positive serum human chorionic gonadotropin measured prior to the first obinutuzumab infusion
38. Known intolerance to MMF *and MPA*

Length of Study

The study will follow all patients for a minimum of *78* weeks after the last infusion of obinutuzumab at Day 182. In consideration of recruitment and follow-up (independent of B-Cell follow-up [BCFU]), the length of study is estimated to be greater than 36 months. Patients may enter BCFU and continue to be evaluated for safety on a limited basis.

End of Study

The study will be considered completed when all patients have completed the Week 104 visit or have completed the required BCFU visits, whichever is longer.

Outcome Measures

Primary Efficacy Outcome Measure

The primary efficacy outcome measure is the proportion of patients who achieve a CRR, evaluated at 52 weeks.

CRR is defined by attainment of all of the following:

39. Normalization of serum creatinine as evidenced by the following:

    Serum creatinine $\leq$ the ULN range of central laboratory values *if baseline (Day 1) serum creatinine is above the ULN*

    Serum creatinine $\leq 15\%$ above baseline and $\leq$ the ULN range of central laboratory values if baseline (Day 1) serum creatinine is $\leq$ *the ULN range of central laboratory values*

    - Inactive urinary sediment (as evidenced by < 10 RBCs/high-power field (HPF) and the absence of red cell casts)
    - Urinary protein to creatinine ratio < 0.5

Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures are the following:

- Proportional analysis of patients who achieve an overall response at Week 52 (CRR + PRR)
- Time to overall response (CRR + PRR) over the course of 52 weeks
- Percent reduction or increase from baseline and mean and median assessments of biomarkers of LN disease activity (e.g., reduction in anti-dsDNA antibody levels, increase C3 and C4 levels)
- Proportion of patients that achieve a PRR at Week 52 as defined by attainment of all of the following:

    Serum creatinine $\leq 15\%$ above baseline value

    No urinary red cell casts and either RBCs/HPF $\leq 50\%$ above baseline *or <10 RBCs/HPF*

50% improvement in the urine protein to creatinine ratio, with one of the following conditions met:

If the baseline urine protein to creatinine ratio is ≤ 3.0, then a urine protein to creatinine ratio of < 1.0

If the baseline protein to creatinine ratio is > 3.0, then a urine protein to creatinine ratio of < 3.0

- Proportion of patients who achieve a CRR at Week 24
- Time to CRR, over the course of 52 weeks.
- Proportion of patients that achieve a modified CRR (mCRR1) at Week 52 employing the primary–efficacy measure definition and removing the urinary sediment analysis criteria

  mCRR1 is defined by attainment of normalization of serum creatinine as evidenced by the following:

  Serum creatinine $\leq$ the ULN range of central laboratory values *if baseline (Day 1) serum creatinine is above the ULN*

  Serum creatinine $\leq 15\%$ above baseline and $\leq$ the ULN range of central laboratory values if baseline (Day 1) serum creatinine $\leq$ *the ULN range* of central laboratory values

  Urinary protein to creatinine ratio < 0.5
- Proportion of patients that achieve a second modified CRR (mCRR2) at Week 52 as defined by attainment of the following:

  Normalization of serum creatinine as evidenced by the following:

  Serum creatinine $\leq 15\%$ above baseline if baseline (Day 1) serum creatinine is above the normal range of the central laboratory values or $\leq$ the ULN range of central laboratory values if baseline (Day 1) serum creatinine is $\leq$ *the ULN range of central laboratory values*

  Inactive urinary sediment (as evidenced by < 10 RBCs/HPF and the absence of red cell casts)

  Urinary protein to creatinine ratio < 0.5
- *Proportion of patients that achieve a third modified CRR (mCRR3) at Week 52 as defined by attainment of the following:*

  Normalization of serum creatine as evidenced by serum creatinine ≤the ULN range of central laboratory values

  Urinary protein to creatinine ratio <0.5

The hierarchical ordering of the secondary endpoints will be pre-specified in the SAP.

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, type, and severity of adverse events
- Abnormal vital signs
- Abnormal laboratory values

Safety will be monitored through regular physical examinations, vital signs, hematologic and chemistry laboratory tests, urinalyses, and incidence and severity of adverse events. In addition, the following will be examined:

- Circulating B cells, T cells, neutrophils and other cell populations
- Plasma immunoglobulins (total Ig, IgG, IgM, and IgA)
- Record of menses
- Pregnancy

- Antibody titers for mumps, rubella, *Varicella*, tetanus, influenza, and *Streptococcus pneumoniae*

Pharmacodynamic Outcome Measure

The primary PD outcome measure for this study is as follows:

- *Changes in levels* of circulating CD19+ B-cells *relative to baseline*

Pharmacokinetic Outcome Measures

The obinutuzumab PK outcome measures for this study are as follows:

Non-linear mixed-effects modeling (with software NONMEM) will be used to analyze the dose concentration−time data of obinutuzumab. The PK profile data will be used to further develop a PK model, including the effect of major covariates (e.g., sex, race/ethnicity, weight, biochemical and hematological parameters at baseline, degree of underlying disease), on the main parameters (e.g., clearance). The derivation of individual measures of exposure, such as area under the concentration-time curve and maximum concentration observed will depend on the final PK model used for this analysis. Results of this analysis may be reported separately. Serum obinutuzumab will be summarized (mean, minimum, maximum, SD, and geometric mean) and reported within this study. Exploratory graphical analyses will be performed to assess whether the occurrences of serious adverse events and abnormalities in the safety laboratory parameters in patients treated with obinutuzumab can be attributed to obinutuzumab exposure. Also, exploratory graphical analyses will be performed to assess whether the variability in response can be attributed to the variability in obinutuzumab exposure. Relevant observed relationships between exposure and safety parameters may be further characterized using different approaches such as logistic regression analysis and indirect response modeling. Additional PK and PD analyses may be conducted as appropriate.

Patient-Reported Outcome Measure

The PRO measure for this study is as follows:

- Subject's Global Assessment

  This visual analog scale (VAS) will be captured in screening, at the baseline visit, and at several timepoints during study conduct.

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- *Changes in levels* of circulating B-cell subsets *relative to baseline*
- *Changes in levels* of exploratory biomarkers, which may include but are not limited to levels of protein and mRNA in serum, *plasma*, blood, and urine, *relative to baseline*
- Proportion of patients experiencing a Systemic Lupus Erythematosus Disease Activity Index-2K flare
- Proportion of patients experiencing a renal flare over 52 weeks and 104 weeks
- Proportion of patients achieving CRR, mCRR1, mCRR2, *and mCRR3* at additional timepoints, including Week 12 and Week 36
- Physician's Global Assessment
- This VAS will be captured in screening, at the baseline visit, and at several timepoints during study conduct.
- *GTCI*
- Renal biopsy evaluations

Investigational Medicinal Products

Test Product (Investigational Drug)

The test product for this study is obinutuzumab and will be administered by IV infusion at a dose of 1000 mg on Days 1, 15, 168, and 182. The study drug will be administered in a hospital or clinic environment where full resuscitation facilities are immediately available and under close supervision of the investigator or designee. After the end of the *first* infusion, the IV line will

remain in place for at least *2 hours* to enable administration of IV drugs if necessary. If no adverse events occur during this period of time, the IV line may be removed. *For subsequent infusions, access through an IV line should remain in place for at least 30 minutes from the end of the infusion, and if no adverse events occur after 30 minutes, the IV access may be removed.*

Comparator (Placebo)

The obinutuzumab placebo (corresponding to the obinutuzumab1000-mg dose) will be administered by IV infusion on Days 1, 15, 168, and 182. The placebo will be administered in a hospital or clinic environment where full resuscitation facilities are immediately available and under close supervision of the investigator or designee. After the end of the *first* infusion, the IV line will remain in place for at least *2 hours* to enable administration of IV drugs if necessary. If no adverse events occur during this period of time, the IV line may be removed. *For subsequent infusions, access through an IV line should remain in place for at least 30 minutes from the end of theinfusion, and if no adverse events occur after 30 minutes, the IV access may be removed.*

Non-Investigational Medicinal Products

After screening, patients who were not already receiving MMF *or MPA* will receive 1500 mg/day *(or equivalent)* in divided doses (2–3 times/day), and all patient doses will be titrated upward to a target dose of 2.0–2.5 g/day *(or equivalent)* in divided doses (2–3 times/day) by Week 4, as tolerated. If reductions in dose are necessary, decreases will be allowed in 250–500 mg *(or equivalent)* decrements. During screening or at randomization, if clinically indicated, patients may receive 750–1000 mg methylprednisolone IV once daily for up to 3 days to treat underlying LN clinical activity. Patients will receive 0.5 mg/kg oral prednisone, tapering this prednisone dose, per protocol, starting on Day 16 and reducing the prednisone dosage to 7.5 mg/day by Week 12.

Prior to each infusion of either study drug or placebo, patients should receive prophylactic treatment with acetaminophen (650–1000 mg) and diphenhydramine (50 mg; or equivalent dose of a similar agent) by mouth, given 30–60 minutes before the start of the infusion period. The patients who are receiving obinutuzumab will receive 80 mg methylprednisolone IV and patients who are receiving placebo will receive placebo-methylprednisolone IV given 30–60 minutes before the start of the obinutuzumab/placebo infusion.

Concomitant Therapy and Clinical Practice

Patients who are not already taking vitamin D (*8*00 IU/day) and calcium supplements (1200 mg/day of calcium citrate or 1500 mg/day of calcium carbonate) will begin taking these supplements at randomization. All patients will take either an ACE inhibitor or an angiotensin-receptor blocker titrated to adequate blood pressure control as recommended by the National Kidney Foundation for chronic kidney disease.

Other agents that affect proteinuria will not be allowed to be initiated during the study. These include but are not limited to the following:

- Non-dihydropyridine calcium antagonists
- Dihydropyridine calcium antagonists
- Aldosterone antagonists
- Direct renin antagonists

Statistical Methods

All efficacy outcomes will be analyzed according to the modified intent-to-treat principle and will include all randomized patients who have received any amount of study drug. Patients will be grouped according to randomized (assigned) treatment, rather than treatment received. Treatment period data will be locked after all patients have completed the Week 52 visit. The primary efficacy and safety analyses will be performed on data for all patients through the Week 52 assessments or early discontinuation.

Safety assessments will be performed on patients who receive study medication. In all safety analyses, patients will be grouped according to the treatment that patients actually received rather than the treatment assigned.

The primary and secondary efficacy analyses will include all randomized patients who received any study medication, with patients grouped according to the treatment assigned at randomization.

Primary Analysis

The primary assessment of efficacy of obinutuzumab, to induce a clinically significant improvement in renal function in patients with ISN/RPS 2003 class III or IV LN, will be assessed by attainment of CRR.

CRR is defined as achievement of all of the following:

- Normalization of serum creatinine as evidenced by the following:

  Serum creatinine $\leq$ the ULN range of central laboratory values if the baseline (Day 1) *serum creatinine is above the ULN*

  Serum creatinine $\leq$ 15% above baseline and $\leq$ the ULN range of central laboratory values if baseline *(Day 1)* serum creatinine is $\leq$ *the ULN range of central laboratory values*
- Inactive urinary sediment (as evidenced by $<$ 10 RBCs/HPF and the absence of red cell casts)
- Urinary protein to creatinine ratio $<$ 0.5

Any patient who switches to rescue medication prior to Week 52 will be considered a non-responder.

The proportions of patients achieving CRR across treatment groups will be compared using a Cochrane-Mantel-Haenzel (CMH) test with race (Afro-Caribbean/African American versus others) and region (United States versus non-United States) as stratification factors. If the test result is in favor of the obinutuzumab group at $\alpha < 0.1$-level (one-sided), it will be concluded that there is a shift toward better renal response associated with the obinutuzumab group.

Determination of Sample Size

This Phase II study is a proof-of-concept study that is designed to detect an improvement in CRR. The primary efficacy endpoint of this study is the proportion of patients that achieve CRR. It is estimated that approximately 30% of patients with proliferative LN who are receiving MMF *(or equivalent)* will achieve a CRR at Week 52 and that the addition of obinutuzumab to MMF *(or equivalent)* will induce an overall CRR rate of 50% at Week 52. On the basis of these assumptions, a total of 120 patients randomized to obinutuzumab- and placebo-treated groups in a 1:1 ratio (60 patients in each of the obinutuzumab- and placebo-treated groups) will yield approximately 83% power at the two-sided $\alpha = 0.2$ significance level using a CMH test, assuming the same CRR proportions across the strata.

Interim Analyses

Pharmacodynamic Futility Interim Analysis

Given the rationale for this study, including the results from the LUNAR and BELONG studies, an interim analysis for futility is planned on the basis of CD19 B-cell counts after 30 patients have been assigned to the obinutuzumab arm and have had their Day 28 blood CD19 B-cell counts assessed by HSFC.

The effect of rituximab on CD19 B-cell counts has been measured by HSFC in an investigator sponsored study in which peripheral B-cell depletion below the lower limit of quantification (LLOQ) of the assay occurred in 46% of patients. Slightly less than half of these rituximab treated patients with full peripheral B-cell depletion achieved a major clinical response, with the remainder of the patients having partial clinical responses. Therefore, it is hypothesized that an improved outcome over rituximab is achievable for a LN patient population with full peripheral Bcell depletion, with the assumption that improved tissue depletion with treatment will parallel the peripheral depletion. To test the hypothesis in this study, we will require at least 50% of the obinutuzumab-treated patients to have peripheral B-cell depletion below the LLOQ of the HSFC assay in order to have a realistic chance of a positive primary endpoint analysis for the treatment arm. Quantification of the link between this biomarker and the study's primary analysis has not been established; therefore predictive probabilities for study statistical significance cannot be provided. Consequently, the study will be terminated if the 5% one-sided Clopper-Pearson upper confidence limit for the proportion of patients who achieve B-cell depletion is not greater than 0.5. Assuming that there are 30 patients at the time of the interim analysis, this will effectively require that ≥ 11 obinutuzumab patients have complete B-cell depletion below the LLOQ of the HSFC assay at the time of the interim analysis.

The interim analysis will be performed by the independent Data Monitoring Committee (iDMC), which may recommend that the study be stopped for futility if the futility criterion is satisfied. Additional criteria for recommending that the study be stopped for futility may be added to the iDMC Charter.

As this interim analysis will only result in termination of the study due to futility, and not for efficacy, an adjustment to the α-level is not required. Although the outcome of the interim analysis may reduce the power of this study to below the estimated 83%, a sample size adjustment has not been made.

Renal Response Interim Analysis

The *iDMC* will conduct an interim efficacy analysis to evaluate renal response when the last patient has achieved the 6-month visit. The interim analysis will be performed and interpreted by members of the iDMC, *who may recommend to the Sponsor the initiation of future study planning, according to rules outlined in the iDMC Charter. If the iDMC does recommend that future study planning can begin, then the summary of renal response data at Week 24 will be shared with appropriate Sponsor senior management personnel who will be unblinded at the treatment group level.* This interim analysis is for planning purposes only and will have no impact on the progression of this study. Consequently, an adjustment to the ・-level is not required.

Appendix 2 Schedule of Assessments

		Treatment Period							
Week	−4 to 0	1	2	4	12	24	26	36	52/ET
Day	−28 to −1	1 [a]	15	28	84	168	182	252	364
Informed consent	x								
Inclusion/exclusion criteria	x	x							
Medical history	x	x							
IxRS assignment [b]	x	x							
Demographic data	x								
Subject's Global Assessment [c]		x		x	x	x		x	x
Physical exam (limited)	x	x				x			x
Height	x								
Vital signs and weight [d]	x	x	x	x	x	x	x	x	x
12-Lead ECG	x								x
Chest X-ray [e]	x								
Physician's Global Assessment		x		x	x	x		x	x
SLICC/ACR assessment	x					x			x
SLEDAI-2K	x	x		x	x	x		x	x
Glucocorticoid Toxicity Change Index		*x*			*x*	*x*			*x*
Hematology [f]	x	x	x	x	x	x	x	x	x
Serum chemistries [g]	x	x	x	x	x	x	x	x	x
Urinalysis [h]	x	x		x	x	x		x	x

Appendix 2 Schedule of Assessments (cont.)

		Treatment Period							
Week	−4 to 0	1	2	4	12	24	26	36	52/ET
Day	−28 to −1	1 [a]	15	28	84	168	182	252	364
24-hour urine collection [i]	*x*	*x*			*x*	*x*		*x*	*x*
Pregnancy test [j]	x	x	x	*x*	*x*	x	x	*x*	x
HBsAg [k], HBcAb, Hepatitis C antibody	x								
Autoantibody profile [l]	x	x		x	x	x		x	x
Antibody titers [m]	x					x			x
Serum PK sampling [n]		x [n]	x [n]	x	x	x [n]	x [n]	x	x
Blood sample for flow cytometry [o]		*x*	x	x	x	x [o]			x
Serum ADAs		x [o]				x [o]			x
Quantitative serum Ig levels (total, IgG, IgM, and IgA)	x	x			x	x			x
C3, C4, CH50 complement	x	x	x	x	x	x		x	x
Serum for biomarkers [o]	x	x [o]	x	x	x	x [o]		x	x
Plasma for biomarkers [o]	*x*	*x* [o]	*x*	*x*	*x*	*x* [o]		*x*	*x*
Urine for biomarkers [p, o]	x	x	x	x	x	x		x	x
PAXgene RNA [o]	x	x [o]	x	x	x	x [o]		x	x
Blood DNA [q] (optional)	x								
Record of menses	x	x	x	x	x	x	x	x	x
Adverse events [r]		x [r]	x [r]	x	x	x [r]	x [r]	x	x

Appendix 2 Schedule of Assessments (cont.)

		Treatment Period							
Week	−4 to 0	1	2	4	12	24	26	36	52/ET
Day	−28 to −1	1 [a]	15	28	84	168	182	252	364
Concomitant medications	x	x	x	x	x	x	x	x	x
Study drug infusion		x [s]	x [s]			x [s]	x [s]		
Corticosteroid dose/taper [t]		x	x	x	x				
Renal biopsy (optional) [u]									(x)

ADA = anti-drug antibody; ET = Early Termination Visit; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; IV = intravenous; IxRS = interactive voice/Web response system; PK = pharmacokinetic; PO = by mouth; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index; SLICC/ACR = Systemic Lupus International Collaborating Clinics/American College of Rheumatology.

Notes: All assessments will be performed pre-infusion unless otherwise specified. Infusion visits (Days 15, 168, and 182) except for Day 1, should be performed within ±3 days of the scheduled visit. Non-infusion visits should be performed within ±3 days of the scheduled visit.

[a] Day 1, unless otherwise notified.

[b] At screening, IxRS will be contacted to obtain assignment of patient screening number. At Day 1, IxRS will be contacted to obtain patient randomization number and drug assignment.

[c] *Subject's* Global Assessment will be performed prior to other assessments.

[d] Blood pressure and pulse rate while patient is seated *for 5 minutes,* and *respiratory rate and* body temperature. Vital signs should be taken pre-infusion, then every 15 minutes for 1 hour, then every 30 minutes until the end of the infusion, and within 30 minutes post-infusion. Additional readings may be obtained at the discretion of the investigator in the event of an infusion-related reaction (e.g., hypotension and/or fever).

[e] If a chest X-ray has been obtained within the past 3 months and no clinically significant abnormality was observed and no new pulmonary signs or symptoms are exhibited, no chest X-ray is required.

[f] Hematology: CBC, RBC count, WBC count and differential, hemoglobin, hematocrit, *mean corpuscular volume, mean corpuscular hemoglobin,* and quantitative platelet count.

[g] Serum chemistries include AST/SGOT, ALT/SGPT, alkaline phosphatase, total protein, albumin, cholesterol, total bilirubin, BUN, uric acid, creatinine, random glucose, lactate dehydrogenase, potassium, sodium, chloride, calcium, phosphorus*, CPK, and triglycerides*. At screening and at unscheduled visits, amylase and lipase will be also included.

Appendix 2 Schedule of Assessments (cont.)

[h] All urinalyses must include microscopic examination, macroscopic urinalysis, and spot urine protein to creatinine ratio (preferably done ~~i~~*o*n the *first* morning *urine*). *T*he spot urine protein to creatinine ratio *on Days 1, 84, 168, 252, and 364* must be done from first-morning urine.

[i] *To be analyzed for total protein, total creatinine, creatinine clearance, and protein to creatinine ratio.*

[j] For women of childbearing potential, including those who have had a tubal ligationPositive test results will be confirmed with a serum pregnancy test. Study drug infusion must not be administered unless the pregnancy test result is negative.

[k] Patients who are HBsAg negative and HBcAb positive with no detectable DNA will be allowed into the study but will require regular monitoring of HBV DNA (see the Laboratory Manual for further details).

[l] Autoantibodies include anti-nuclear antibody, anti-dsDNA, Sm, Ro, La, RNP*, and anti-C1q*.

[m] Antibody titers include mumps, rubella, *Varicella*, tetanus, influenza, and *S. pneumoniae.*

[n] Obtain pre-infusion (within 30 minutes prior to the start of infusion) and at the end of infusion (or within 30 minutes after the end of infusion).

[o] Samples will be drawn before administration of study drug on dosing days.

[p] Urine for biomarkers will be processed at the study site. Instructions will be provided in the laboratory manual.

[q] The DNA samples are optional and should only be obtained from patients who sign the separate Roche Clinical Repository Informed Consent Form. *Preferably, samples will be obtained at screening visit, but they may be obtained at subsequent study visits.*

[r] On Day 1, adverse events will be recorded during infusion and post-infusion. For Days 15, 168, and 182, adverse events will be recorded pre-infusion, during infusion, and post-infusion. For all serious infectious adverse events reported, CBC with differentials, quantitative Ig, and CD19 B-cell counts should be determined within 1 week of onset.

[s] On Days 1, 15, 168, and 182, administer 80 mg methylprednisolone IV (or placebo), 650–1000 mg acetaminophen PO, and 50 mg diphenhydramine PO (or other antihistamine) 30–60 minutes prior to the study-drug infusion.

[t] Patients may initiate 0.5 mg/kg/day oral prednisone in screening or at Day *2*. Oral corticosteroid taper will begin on Day 16. The maximum allowable daily dose of prednisone will be 60 mg.

[u] All patients will be asked to undergo an optional repeat renal biopsy after completion of the treatment portion of the study (after Week 52). If a patient agrees to a repeat renal biopsy, one should be performed within 4 weeks of completion of the treatment portion of the study. Biopsies performed at other times, for clinical reasons, will also be submitted for central review. Because examination of the biopsy sample may potentially unblind the study treatment, investigators and study site personnel should not examine the biopsy sample for immunohistochemistry of B cells or be informed of its results.

Appendix 3 Imputation Rules for Partial or Missing Dates

	Start Date/Time	End Date/Time
Concomitant Medications	Partially Missing **Day**: First day of the month (i.e., 01) **Month**: January **Year**: No imputation **Seconds**: 00 **Minutes**: 00 **Hours**: 00 Completely Missing **Date**: No imputation **Time**: 00:00:00 **Note**: if end time is available and start/end dates are equal and the imputed start time is after end time then impute start time with end time	Partially Missing **Day**: Last day of the month **Month**: December **Year**: No imputation **Seconds**: 59 **Minutes**: 59 **Hours**: 23 Completely Missing **Date**: No imputation **Time**: 23:59:59
Medical History	Partially Missing **Day**: First day of the month (i.e., 01) **Month**: January **Year**: No imputation **Seconds**: 00 **Minutes**: 00 **Hours**: 00 Completely Missing **Date**: No imputation **Time**: 00:00:00 Note: if end time is available and start/end dates are equal and the imputed start time is after end time then impute start time with end time	Partially Missing **Day**: Last day of the month **Month**: December **Year**: No imputation **Seconds**: 00 **Minutes**: 00 **Hours**: 00 Completely Missing **Date**: No imputation **Time**: 00:00:00

Appendix 3 Imputation Rules for Partial or Missing Dates (cont.)

Laboratory	Partially Missing **Day**: No imputation **Month**: No imputation **Year**: No imputation **Seconds**: 59 **Minutes**: 59 **Hours**: 23 Completely Missing **Date**: No imputation **Time**: 23:59:59	Partially Missing **Day**: No imputation **Month**: No imputation **Year**: No imputation **Seconds**: 59 **Minutes**: 59 **Hours**: 23 Completely Missing **Date**: No imputation **Time**: 23:59:59
Adverse Events	Partially Missing **Day**: If the MM-YYYY of start date is not equal to the MM-YYYY of first treatment date then set to 01-MM-YYYY. If the MM-YYYY of start date is equal to the MM-YYYY of first treatment date then if the end date is ≥ date of first treatment set to max(01-MM-YYYY, date of first treatment) , otherwise if end date < date of first treatment set to 01-MM-YYYY. **Month**: Set to max(01-01-YYYY, date of first treatment). **Year**: Set to start date of first treatment. **Seconds**: 59 **Minutes**: 59 **Hours**: 23 Completely Missing Set to start date of first treatment. Note: For all imputations above, if the resulting imputed start date is after the end date then set start date to end date.	Partially Missing **Day**: Set to last day of the month, unless the outcome is death in which case impute with min(last day of month, date of death) **Month**: December, unless the outcome is death in which case impute with min(DD-12-YYYY, date of death) **Year**: If the outcome is death then impute with the date of death, otherwise no imputation. **Seconds**: 59 **Minutes**: 59 **Hours**: 23 Completely Missing If the outcome is death then impute with the date of death, otherwise no imputation.