

**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

**NCT Number:** NCT02550652

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## PROTOCOL

**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:** 4

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**TEST PRODUCT:** Obinutuzumab (GA101; RO5072759)

**NCT NUMBER:** NCT02550652

**SPONSOR:** F. Hoffmann-La Roche Ltd

**APPROVAL DATE:** See electronic signature and date stamp on the final page of this document.

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## PROTOCOL HISTORY

Protocol	
Version	Date Final
4	See electronic date stamp on final page.
3	2 February 2016
2	24 July 2015
1	6 May 2015

## PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Protocol WA29748 has been amended primarily to update the details for the end of the study. Substantial changes to the protocol, along with a rationale for each change, are summarized below:

- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol (front matter and Section 5.4.1). Medical Monitor contact information has been replaced with a sentence indicating that this information will be provided separately to sites.
- The description of the end of study has been updated to emphasize that it is defined as the last patient's last visit at Week 104 when B-cell follow-up (BCFU) visits for all patients will end. This represents a minimum of 78 weeks (~18 months) of safety follow-up after the last dose of study drug to assess the occurrence of adverse events and to enable an assessment of peripheral blood CD19+ B cell return. An analysis of the relationship between obinutuzumab exposure and B-cell count for patients with Lupus Nephritis (LN) in this study (WA29748) who have already completed 18-months of follow-up has been performed and shows that the vast majority of patients recovered or repleted their B-cells by 18 months after their last obinutuzumab dose, while a small percentage of patients experienced prolonged B-cell depletion. During the extended B-cell depletion period, the safety profile of patients under follow-up was consistent with the overall safety profile observed up until Week 104. This finding is in-line with considerable experience with other anti-CD20 antibodies with the same mechanism of action in autoimmune diseases (Section 3.2).
- The reporting of the term "sudden death" has been updated to also require the presumed cause of death (Section 5.3.5.8).
- Adverse event reporting for hospitalization has been clarified (Section 5.3.5.11).
- The Sponsor record retention policy has been clarified (Section 7.5).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with CTR requirements (Section 8.4).
- The process for reviewing and handling protocol deviations has been updated per internal standard operating procedures (Section 9.2).
- Due to certain local requirements and an alignment of Sponsor process, it has been clarified that summaries of clinical study results may be available in health authority databases for public access in addition to redacted Clinical Study Reports (Section 9.5).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in *italics*. This amendment represents cumulative changes to the original protocol.

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## PROTOCOL AMENDMENT ACCEPTANCE FORM

**TITLE:** A RANDOMIZED, DOUBLE-BLIND,  
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TO EVALUATE THE SAFETY AND EFFICACY OF  
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**TEST PRODUCT:** Obinutuzumab (GA101; RO5072759)

**SPONSOR:** F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

---

Principal Investigator's Name (print)

---

Principal Investigator's Signature

---

Date

Please retain the signed original of this form for your study files. Please return a copy as instructed by your local study monitor.

## 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

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**IND NUMBER:** 125,054

**NCT NUMBER:** NCT02550652

**TEST PRODUCT:** Obinutuzumab (GA101; RO5072759)

**PHASE:** II

**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:

- 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:

- 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
- To characterize the immunogenic potential of obinutuzumab by measuring human anti-drug antibodies and assessing their relationship with other outcome measures
- 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:

- 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<sup>2</sup> 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:

- Signed Informed Consent Form
- Age 18–75 years
- Ability to comply with the study protocol, in the investigator's judgment
- Diagnosis of SLE, according to current ACR criteria (at least four criteria must be present, one of which must be a positive ANA)
- 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.
- Proteinuria (urine protein to creatinine ratio) >1.0, based on a 24-hour urine collection
- 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.

- 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:

- 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
- 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.
- Severe renal impairment as defined by estimated GFR  $< 30$  mL/min or the need for dialysis or renal transplant
- Greater than 50% of glomeruli with sclerosis on renal biopsy
- Treatment with cyclophosphamide or calcineurin inhibitors within the 3 months prior to randomization
- 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
- Lack of peripheral venous access
- Pregnancy or lactation
- History of severe allergic or anaphylactic reactions to monoclonal antibodies or known hypersensitivity to any component of the obinutuzumab infusion
- 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
- 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
- Known HIV infection
- 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
- History of serious recurrent or chronic infection
- 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)
- Currently active alcohol or drug abuse or history of alcohol or drug abuse within 52 weeks prior to screening
- Major surgery requiring hospitalization within 4 weeks of randomization (excluding diagnostic surgery)
- Previous treatment with an anti-CD20–targeted therapy within 12 months of randomization
- Previous treatment with a biologic B-cell–targeted therapy (other than anti-CD20) within 6 months of randomization
- Treatment with any investigational agent within 28 days of randomization or five half-lives of the investigational drug (whichever is longer)
- Receipt of a live vaccine within 28 days prior to screening
- Intolerance or contraindication to oral or IV corticosteroids
- Aspartate aminotransferase or alanine aminotransferase  $> 2.5 \times$  upper limit of normal (ULN)

- Amylase or lipase  $>2 \times$  ULN
- Neutrophils  $<1.5 \times 10^3/\mu\text{L}$
- 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.
- Hemoglobin  $<7 \text{ g/dL}$ , unless caused by autoimmune hemolytic anemia resulting from SLE
- Platelet count  $<10,000/\mu\text{L}$
- Positive serum human chorionic gonadotropin measured prior to the first obinutuzumab infusion
- 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 end of this study is defined as the last patient's last visit at Week 104. This has been selected to enable 78 weeks (~18 months) of safety follow-up after the last dose of study drug to assess the occurrence of adverse events and to enable an assessment of peripheral blood CD19+ B cell return.

Additional B-cell follow-up (BCFU) visits will occur until patients have achieved their baseline CD19+ count or achieved 25 cells/ $\mu\text{L}$  CD19+ count (the lower limit of normal (LLN) of CD19+ B cells for this lupus population), whichever occurs first. B-cell follow-up (BCFU) visits for all patients will end when the last patient has completed ~18 months of safety follow-up from the last dose of blinded obinutuzumab infusion.

Patients who receive additional therapies that reduce peripheral B-cell counts will not be included in BCFU.

### 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:

- 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  $< 10 \text{ RBCs}/\text{high-power field (HPF)}$  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  $\leq 3.0$ , 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 creatinine as evidenced by serum creatinine  $\leq$  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 obinutuzumab 1000-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 the infusion, 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 (800 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 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  $\geq 11$  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  $\alpha$ -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  $\alpha$ -level is not required.

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACE	angiotensin-converting enzyme
ACR	American College of Rheumatology
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ALMS	Aspreva Lupus Management Study
ANA	anti-nuclear antibody
ARB	angiotensin-receptor blocker
AUC	area under the concentration–time curve
BAFF	B-cell activating factor
BCFU	B-cell follow-up
CDC	complement-dependent cytotoxicity
CLL	chronic lymphocytic leukemia
C <sub>max</sub>	maximum concentration observed
CMH	Cochrane-Mantel-Haenzel
CRR	complete renal response
EC	Ethics Committee
eCRF	electronic case report form
EDC	electronic data capture
ESRD	end-stage renal disease
GC	germinal center
GFR	glomerular filtration rate
GI	gastrointestinal
GTCI	Glucocorticoid Toxicity Change Index
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HIPAA	Health Insurance Portability and Accountability Act
HPF	high-power field
HSFC	high-sensitivity flow cytometry
ICH	International Conference on Harmonisation
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
IRR	infusion-related reaction
ISN	International Society of Nephrology
IV	intravenous

Abbreviation	Definition
IxRS	interactive voice/Web response system
LLN	lower limit of normal
LLOQ	lower limit of quantification
LN	lupus nephritis
mAb	monoclonal antibody
mCRR1	modified complete renal response
mCRR2	second modified complete renal response
mCRR3	third modified complete renal response
MMF	mycophenolate mofetil
MOA	mechanism of action
MPA	mycophenolic acid
NaCl	sodium chloride
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin's lymphoma
NK	natural killer
NSAID	nonsteroidal anti-inflammatory drug
PD	pharmacodynamic
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PRO	patient-reported outcome
PRR	partial renal response
RCR	Roche Clinical Repository
RPS	Renal Pathology Society
SAP	Statistical Analysis Plan
SLE	systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus International Collaborating Clinics
TI	tubulointerstitial inflammation
ULN	upper limit of normal
VAS	visual analog scale

## **1. BACKGROUND**

### **1.1 BACKGROUND ON LUPUS NEPHRITIS**

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease that occurs primarily in women of childbearing age. It is characterized by multisystem involvement and immunological abnormalities, and much of the tissue damage is thought to occur through autoantibody formation and immune complex deposition. The disease is heterogeneous in its clinical presentation, course, and prognosis. However, most patients present with joint involvement, skin rashes, mouth ulcers, Raynaud's phenomenon, and/or severe fatigue. Inflammation of pericardial and pleural tissues may also be present. The most serious manifestations include CNS and renal involvement, which correlate with poor outcomes that include temporary or permanent disability or death. Typically, the disease follows a relapsing-remitting course with intermittent periods of disease activity (flare) interspersed with periods of relative quiescence.

The incidence and prevalence of SLE varies with sex, race, and ethnicity. The estimated prevalence of SLE in the United States ranges between 65 and 155 per 100,000 (Walsh et al. 2001; Ward 2004; Naleway et al. 2005; Chakravarty et al. 2007; Molina et al. 2007; Sacks et al. 2010; Feldman et al. 2013; Furst et al. 2013; Lim et al. 2014). In adulthood, approximately nine times as many women as men are affected. The disease has a higher incidence and worse outcome among African-Americans, Afro-Caribbeans, Hispanics, and Asians compared with Caucasians.

Medications for the successful treatment of SLE as measured by long-term remission are limited, and only one new medication for SLE treatment has been approved in more than 50 years (Burness and McCormack 2011). Analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) provide partial symptomatic relief. Anti-malarial drugs are generally well tolerated by patients with SLE and appear to have a beneficial effect on the prevention of lupus flares, increasing long-term survival, and possibly ameliorating certain types of organ damage (Ruiz-Irastorza et al. 2009). However, these agents are generally regarded as having insufficient efficacy for moderate to severe manifestations of SLE.

The mainstays of therapy for more significant manifestations of SLE are corticosteroids and off-label use of immunosuppressive drugs (e.g., methotrexate, mycophenolic acid [MPA] [as either mycophenolate mofetil (MMF) or Myfortic® (MPA as sodium salt)], azathioprine, and cyclophosphamide), which have profound and diverse effects on the immune system in patients with lupus. However, the use of these immunosuppressant agents is limited by their safety profiles. Corticosteroids, for example, are effective for many of the manifestations of SLE but have significant short- and long-term adverse effects, including infections, osteoporosis, hyperglycemia, and hyperlipidemia.

Lupus nephritis (LN) is a common manifestation of SLE and continues to be a major cause of morbidity and mortality in this patient population. Of unselected patients with

SLE, 25%–50% have abnormalities of urine or renal function early in the course of their disease, and up to 60% of adults and 80% of children may eventually develop overt renal abnormalities (Cameron 1999). Proteinuria is the most common feature of LN, often in the nephrotic range, and is frequently accompanied by a worsening of renal function. The clinical course of LN varies from mild subclinical disease to an aggressive course that may progress to end-stage renal disease (ESRD) (Flanc et al. 2004). This is particularly concerning because patients with LN, despite having a decrease in clinical lupus activity after they begin renal replacement therapy, have been noted to have poorer outcomes than other patients with non-lupus causes of ESRD (Lee et al. 2003).

The nature and severity of the clinical features do not always predict the underlying histological severity, and renal biopsy is necessary for a precise diagnosis. The findings from a consensus conference in 2002 on renal pathology in LN were adopted by the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) leading to the ISN/RPS 2003 classification system (Weening et al. 2004). This classification scheme grades LN on the basis of histological features seen using light microscopy (see [Table 1](#)).

**Table 1 International Society of Nephrology/Renal Pathology Society 2003 Classification of Lupus Nephritis**

Class I	Minimal mesangial LN
Class II	Mesangial proliferative LN
Class III	Focal LN (<50% of glomeruli) <ul style="list-style-type: none"> <li>III (A): active lesions</li> <li>III (A/C): active and chronic lesions</li> <li>III (C): chronic lesions</li> </ul>
Class IV	Diffuse LN (≥50% glomeruli) <ul style="list-style-type: none"> <li>Diffuse segmental (IV-S) or global (IV-G) LN</li> <li>IV (A): active lesions</li> <li>IV (A/C): active and chronic lesions</li> <li>IV (C): chronic lesions</li> </ul>
Class V	Membranous LN
Class VI	Advanced sclerosing LN (≥90% globally sclerosed glomeruli without residual activity)

LN = lupus nephritis.

Note: Class V may occur in combination with Class III or IV, in which case both will be diagnosed.

Source: Markowitz GS, D'Agati VD. The ISN/RPS 2003 classification of lupus nephritis: an assessment at 3 years. *Kidney Int* 2007;71:491–5.

Cyclophosphamide, MMF or MPA, and azathioprine, along with corticosteroids, have been used in the treatment of proliferative Class III/IV LN with varying degrees of success and varying adverse effects (Houssiau et al. 2004). Cyclophosphamide became a dominant standard of care in the 1980s, yet acute and dose-limited toxicity prompted the investigation of lower-dose regimens such as the Euro-lupus regimen (Houssiau et al. 2002). Toxicity also prompted the search for new therapies, including MMF (Chan et al. 2000; Ginzler et al. 2005), and a study that directly compared the two therapies (Contreras et al. 2004). Given the organ-threatening severity of LN, placebo-controlled studies were not considered to be appropriate to prove the efficacy of either agent, and both cyclophosphamide and MMF became unapproved standards of care (Hahn et al. 2012).

A major advance in the treatment of patients with LN was the demonstration that MMF was comparable in efficacy and safety to cyclophosphamide in the Aspreva Lupus Management Study (ALMS) (Appel et al. 2009) and potentially superior to azathioprine in remission maintenance (Dooley et al. 2011). These critical studies solidified the place of MMF as a potentially effective therapy for LN, although MMF was not found to be superior to cyclophosphamide. Both MMF and cyclophosphamide are considered to be first-line therapies for the treatment of patients with proliferative LN, as outlined in the American College of Rheumatology (ACR) Lupus Nephritis Guidelines (Hahn et al. 2012).

As a measure of unmet need, the risk of mortality remains elevated for patients with lupus. In the modern era, on the basis of a multisite international cohort of 9500 patients with lupus, the standardized mortality ratio was 2.4, with particularly high mortality seen with renal disease (Bernatsky et al. 2006). Among patients with LN, 10%-30% of patients progress to ESRD despite aggressive immunosuppressive therapy (Costenbader et al. 2011). Whereas these outcomes have improved over the past 30 years, continued risk of treatment failure remains (as defined by death, ESRD, sustained doubling of serum creatinine, LN flare, or need for rescue medications), which ranges 14.5%-20.1% per 100 patient-years over the course of follow-up (Dooley et al. 2011; Rovin et al. 2012).

## 1.2 BACKGROUND ON OBINUTUZUMAB

Obinutuzumab (also known as GAZYVA or GA101) is a recombinant, monoclonal, humanized, and glycoengineered type II CD20 antibody of the IgG1 isotype that specifically targets the extracellular loop of the CD20 transmembrane antigen that is expressed on the surface of non-malignant and malignant pre-B and mature B lymphocytes but not on hematopoietic stem cells, pro-B cells, normal plasma cells, or other normal tissue (Mössner et al. 2010; Niederfellner et al. 2011; Klein et al. 2013). Glycoengineering of the Fc portion of obinutuzumab results in a higher affinity for FcgRIII receptors on immune effector cells such as natural killer (NK) cells and macrophages/monocytes (Mössner et al. 2010).

Obinutuzumab in combination with chlorambucil is currently approved in multiple countries worldwide for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL).

Data from an estimated 3284 patients, up to 31 October 2014, are available for safety analysis of obinutuzumab in clinical studies. These data include patients with CLL or non-Hodgkin's lymphoma (NHL) from doses of 50–2000 mg in monotherapy or in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone; fludarabine plus cyclophosphamide; bendamustine; or chlorambucil.

Nonclinical in vitro studies show that obinutuzumab mediates superior induction of direct cell death and effector cell-mediated antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody dependent cellular phagocytosis on a panel of NHL cell lines compared with the type I CD20 antibodies rituximab and ofatumumab. Conversely, its potency to mediate complement-dependent cytotoxicity (CDC) is significantly reduced compared with these two antibodies. In ex vivo autologous whole-blood B-cell depletion studies with blood from healthy volunteers as well as patients with CLL, obinutuzumab mediated superior B-cell depletion when compared with rituximab.

These properties of obinutuzumab translated into superior anti-tumor efficacy in direct comparison with rituximab against a number of aggressive subcutaneous and disseminated NHL xenograft models. The efficacious and optimal dose range of obinutuzumab in xenograft models ranged 10–30 mg/kg, corresponding to trough levels of 300–600 µg/mL. Treatment with obinutuzumab resulted in potent and superior depletion of B-cells in the peripheral blood and in lymphoid tissues of hCD20 transgenic mice and cynomolgus monkeys. Vaccination studies in cynomolgus monkeys and human CD20 transgenic mice showed that the enhanced efficacy in terms of the B-cell depletion of obinutuzumab translated into suppression of de novo antibody responses but left the protective humoral memory responses intact.

The data generated to date imply that obinutuzumab represents a novel therapeutic anti-CD20 antibody with outstanding efficacy compared with classical type I and non-ADCC-enhanced anti-CD20 antibodies, such as rituximab, ocrelizumab and ofatumumab.

See the immunology Obinutuzumab Investigator's Brochure for additional details on nonclinical and clinical studies of obinutuzumab.

### **1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT**

Multiple studies have demonstrated histopathologic involvement of B and T cells in LN pathogenesis. A temporal model established from lupus-prone mice strains with nephritis suggests that autoantibodies and immune complexes deposit within the glomerular basement membrane of the kidney, fix complement, and cause local inflammation. Lymphocytes, macrophages, and neutrophils migrate into the kidney and

establish continued tubulointerstitial inflammation (TI) that triggers proliferative mesangial changes in the glomeruli with resultant proteinuria, hematuria, and altered renal function. This experimental nonclinical model demonstrates antibody-producing cells (APCs) that mature into plasma cells (Cassese et al. 2001). As an organized immunologic reaction involving B cells, T cells, macrophages, and supporting dendritic cells becomes amplified, renal function further deteriorates and is fatal in multiple mouse models.

The presence of B cells in LN has been better characterized over the past 10 years (Steinmetz et al. 2008; Lee and Ballow 2010). Recently, Chang et al. (2011) published an extensive histopathologic review of LN biopsy samples from a longitudinal series of patients at the University of Chicago. This review confirms the presence of B cells in LN biopsies and describes their organization into T:B-cell aggregates and germinal centers (GCs). The review also confirmed that TI is an important pivotal variable and an independent risk factor in predicting renal outcomes in patients with LN (Hill et al. 2000; Alsuwaida et al. 2013). On renal biopsy, the presence and degree of TI is prognostic and may identify those patients with LN who are at risk for progression to renal failure (Schwartz et al. 1982; Esdaile et al. 1989; Hsieh et al. 2011). As such, TI is a central manifestation of LN that might arise from different pathogenic mechanisms from those implicated in glomerulonephritis, and it may serve as a potential therapeutic target in this disease.

These data, demonstrating the presence of B cells in LN, implicate tertiary lymphoid neogenesis in the pathogenesis of lupus TI. The presence of lymphoid-like structures strongly correlated with detectable tubular basement membrane immune complexes. These observations suggested that in LN, GCs, and T:B aggregates select for cells that locally secrete pathogenic antibodies in the tubulointerstitium. Furthermore, the data indicated that such plasmablast foci are a usual feature of LN that is complicated by severe TI. Although interstitial inflammation often correlates with the extent of glomerular injury in LN, there are several lines of evidence that these processes may be distinct. Chang et al. (2011) hypothesized that identification of the *in situ* antigens and factors promoting local B-cell selection and expansion of organized immunological structures in the interstitium should yield important biomarkers and could lead to novel therapeutic strategies in LN. Anti-vimentin autoantibodies are being investigated as a potentially pathogenic autoantibody produced by vimentin expression in the damaged interstitium (Kinloch et al. 2014).

Genentech and Roche have experience conducting LN clinical studies with two anti-CD20 compounds: rituximab and ocrelizumab. Study U2790g (the LUNAR study; Rovin et al. 2012) was a randomized, parallel arm, add-on double-blind placebo-controlled study in patients with Class III and IV proliferative LN. The study evaluated the regimen of rituximab plus MMF versus MMF in combination with methylprednisolone infusions and a prednisone taper and enrolled 144 adult patients in North and South America. The study failed to meet its primary endpoint of overall

response (weighted toward complete renal response [CRR]); no major new safety signals were identified. The LUNAR study determined that the combination of rituximab + MMF was more effective at reducing anti-dsDNA autoantibody levels and increasing complement levels than MMF alone. In addition, there was a 15.3% increase of partial renal response (PRR) with rituximab, and fewer patients in the rituximab arm required rescue with cyclophosphamide (n=1) versus the MMF-alone arm (n=8). A pre-specified sub-analysis of African American patients (n=40) demonstrated that 70% of these patients responded (PRR+CRR) in the rituximab arm versus 45% in the MMF-alone arm (p=0.2) (Rao et al. 2012). This analysis clarified that non-responders had higher mean serum creatinine levels, a higher degree of proteinuria, and higher mean blood pressure than did responders.

The partial response observed in the LUNAR study, in addition to the multiple publications that suggest partial response in patients with more refractory disease (Lu et al. 2009; Jónsdóttir et al. 2010; Roccatello et al. 2011; Turner-Stokes et al. 2011; Díaz-Lagares et al. 2012; Gregersen and Jayne 2012; Furtado and Isenberg 2013), particularly with the combination of rituximab and cyclophosphamide (Ng et al. 2007), has suggested that rituximab has a place in the treatment of these patients and led to its incorporation into the ACR LN Treatment Guidelines in 2013 (Hahn et al. 2012). This partial response difference along with the improvement in anti-dsDNA antibody and complement levels suggests that the drug has activity, but not at the level of CRR. These findings, in addition to lupus-related factors described below that might impair rituximab's ability to deplete B cells in SLE, are consistent with the hypothesis that incomplete local B-cell depletion contributed to a partial response and that a more efficient B-cell depleting agent (obinutuzumab) might be associated with greater efficacy.

A PRR improvement was also observed in a second company-sponsored study of LN, Study WA20500 (the BELONG study; Mysler et al. 2013). The BELONG study was a Phase III dose-ranging study that evaluated ocrelizumab, a humanized anti-CD20 monoclonal antibody (mAb) therapy with 3–5-fold greater ADCC than rituximab. The BELONG study enrolled 350 patients in an international, double-blind, randomized, controlled dose-ranging study enrolling Class III and Class IV patients with LN who were treated with a background therapy of either MMF or Euro-Lupus-regimen cyclophosphamide (500 mg intravenous [IV] every 2 weeks × 6 doses). This study was terminated because of a minor imbalance of serious infectious events (largely confined to countries in Asia) and after the LUNAR study data became available, suggesting that the likelihood of a positive outcome had decreased significantly.

There were several notable findings from the BELONG study. Ocrelizumab was associated with a 12.2% increase in overall response (66.9%) across both doses and background treatments compared with controls (54.7%). In the Euro-Lupus regimen-cyclophosphamide-treated patients, ocrelizumab was associated with a 22.7% increase in overall response (65.6%) across both doses compared with the control (42.9%). Serious infectious events were clustered within the first 12 weeks of the study,

consistent with the time of maximal prednisone exposure. Lastly, ocrelizumab was associated with a significant decrease in anti-dsDNA antibody levels and an improvement in complement levels compared with the controls. These findings replicate the efficacy and immunologic outcomes from the LUNAR study and are consistent with the hypothesis that patients with LN are resistant to B-cell depletion and that anti-CD20 therapy is associated with PRR.

There are available data that demonstrate that achievement of CRR is prognostic of a good long-term outcome (Chen et al. 2008); however, across the LUNAR and BELONG studies, only 30%–40% of patients were able to achieve CRR at 12 months. In the LUNAR study (Rovin et al. 2012), 54% of the patients who were randomized to the high-dose MMF/high-dose prednisone arm achieved no response, defined as failure to achieve PRR or CRR or having met another definition of treatment failure. Recently, efforts have been made to identify subsets of patients treated with either Euro-Lupus cyclophosphamide (Houssiau et al. 2004) or MMF (Dall'Era et al. 2011) who achieve a short-term favorable outcome and are of potentially lower unmet medical need. The putative biomarkers from the ALMS database that predict good response are baseline C4 level, duration of diagnosis, baseline estimated glomerular filtration rate (GFR), early normalization of complement, and reduction of proteinuria by  $\geq 25\%$  from baseline (Dall'Era et al. 2011). Other clinical prognostic factors such as non-Caucasian race, poor socioeconomic status, uncontrolled hypertension, high activity and chronicity score (on biopsy), baseline renal impairment, nephritic relapses, and poor initial therapy response have been associated with a poor outcome and thus higher unmet need. With these factors in mind, a significantly high proportion of patients have poor prognostic factors and exhibit major unmet medical needs despite currently available therapies. A recent review of 73 patients undergoing renal biopsy for LN concluded that persistence of interstitial inflammation is also associated with poor long-term outcome, yet few patients receive repeat renal biopsies, suggesting that unrecognized, uncontrolled inflammation may be present in many patients (Alsuwaida 2013). Existing therapies have known toxicities that can limit their use, and prednisone toxicity is increasingly recognized as a major concern with standard induction regimens (Petri et al. 2014). Higher rates of CRR, faster achievement of CRR, improved tolerability of drugs, significant reduction of prednisone exposure, and reduction of flares in maintenance stages have currently not been achieved.

The scientific rationale for the experimental use of obinutuzumab in LN is supported by multiple experiments that suggest that patients with SLE are resistant to B-cell depletion with rituximab, as described below. SLE is considered a classic autoimmune disease marked by a loss of B-cell tolerance (Rahman and Isenberg 2008). There are multiple publications that document the presence of B cells in active LN, both from experimental mouse models of lupus (Cassese et al. 2001) and also from more recent surveys of LN histopathology (Chang et al. 2011). This evidence demonstrates a primary role for

B cells in disease pathogenesis; however, two studies using anti-CD20 therapies in LN (the LUNAR and BELONG studies) demonstrated only partial responses.

Recent data suggest that B cells are resistant to and are incompletely depleted by rituximab in the peripheral blood of patients with SLE (Vital et al. 2011). The explanation for this finding may be related to the putative mechanisms of actions (MOAs) of rituximab—the indirect depletion of CD20+ B cells by ADCC and CDC and via apoptotic mechanisms, as well as new information that all three may be impaired in patients with lupus.

ADCC and the interaction between the Fc portion of rituximab and the effector cell may be altered in SLE (Ahuja et al. 2011). CDC may be impaired by the hypocomplementemic environment of LN, and the role of complement in B-cell depletion of patients with SLE has not been formally studied (Leffler et al. 2014). Apoptotic defects are known to occur in SLE (Bouts et al. 2012), and this resistance to normal cellular death may translate to incomplete B-cell killing with rituximab via this mechanism. In addition, the elevated human anti-chimeric antibody rates that were observed in the rituximab lupus studies and the early peripheral B-cell return that was repeatedly demonstrated in patients with SLE who were treated with rituximab is further evidence that rituximab may not have fully depleted B cells in these studies.

Obinutuzumab is a humanized, type II anti-CD20 mAb that has been approved for CLL and was demonstrated in clinical studies to be superior to rituximab (Dooley et al. 2011). Obinutuzumab exhibits direct B-cell killing through a type II mechanism (Honeychurch et al. 2012) and has significantly higher ADCC compared with either rituximab or ocrelizumab, a type I humanized anti-CD20 mAb (see the Obinutuzumab Investigator's Brochure). Obinutuzumab has lower CDC and less dependence on complement for its MOA. There are recent data that suggest that obinutuzumab may show depletion of B cells superior to rituximab in lupus-prone mouse models (unpublished data on file) and in patients with lupus (in an in vitro peripheral blood mononuclear cells analysis of B cells) (Reddy et al. 2014). With consideration of these combined data, this scientific rationale supports the Phase II evaluation of obinutuzumab in patients with LN.

Given the high unmet medical need of patients with LN for an improved CRR rate and therefore reduced risk of ESRD, achievement of this benefit is desirable. The known risk of obinutuzumab, as characterized in the CLL-11 Stage 2 head-to-head study of obinutuzumab versus rituximab (Goede et al. 2014), suggests that its risk profile is comparable to rituximab, with the exception of worsened infusion-related reactions (IRRs). In this setting, the benefit-risk assessment favors conducting this Phase II randomized clinical study.

## **2. OBJECTIVES**

### **2.1 EFFICACY OBJECTIVES**

The primary efficacy objective for this study is as follows:

- To evaluate the efficacy of obinutuzumab compared with placebo in patients with ISN/RPS Class III or IV LN as measured by CRR at 52 weeks

The secondary efficacy objectives for this study are as follows:

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

### **2.2 SAFETY OBJECTIVES**

The safety objectives for this study are as follows:

- 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
- To characterize the immunogenic potential of obinutuzumab by measuring human anti-drug antibodies (ADAs) and assessing their relationship with other outcome measures
- To fully characterize adverse events of special interest, including infusion reactions, infections, thrombocytopenia, and neutropenia

### **2.3 PHARMACODYNAMIC OBJECTIVE**

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

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

### **2.4 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 MMF

### **2.5 PATIENT-REPORTED OUTCOME OBJECTIVE**

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

## **2.6 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).

## **3. STUDY DESIGN**

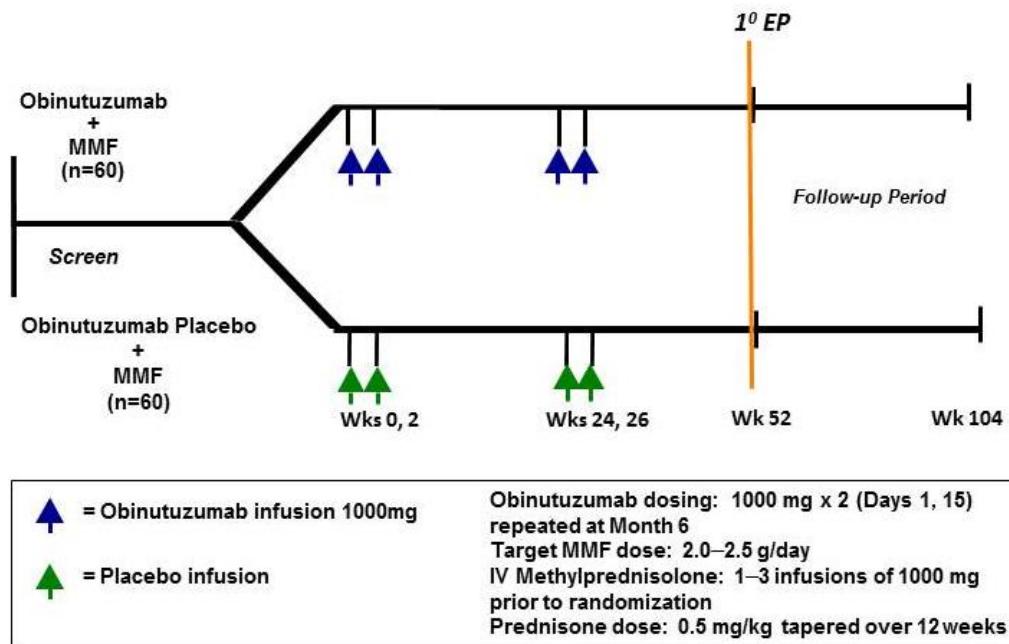
### **3.1 DESCRIPTION OF STUDY**

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 SLE based on current 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 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 (see [Table 1](#)) 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 GFR <30 mL/minute per 1.73 m<sup>2</sup> of body surface area), ESRD requiring dialysis or transplantation, evidence of active infections, and other safety-related exclusions. Patients will receive an initial 1000 mg of methylprednisolone 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 IRRs. Oral corticosteroids will be initiated at a dose of 0.5 mg/kg (maximum 60 mg/day) and will be reduced over 10 weeks (see [Appendix 5](#)). 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 (Bichile and Petri 2014). 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 (Condon et al. 2013).

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.

**Figure 1 Study Schema**



EP=endpoint; MMF=mycophenolate mofetil.

### **3.2 END OF STUDY**

*The end of this study is defined as the last patient's last visit at Week 104. This has been selected to enable 78 weeks (~18 months) of safety follow-up after the last dose of study drug to assess the occurrence of adverse events and to enable an assessment of peripheral blood CD19+ B cell return.*

*Additional B-cell follow-up (BCFU) visits will occur until patients have achieved their baseline CD19+ count or achieved 25 cells/µL CD19+ count (the lower limit of normal (LLN) of CD19+ B cells for this lupus population), whichever occurs first. B-cell follow-up (BCFU) visits for all patients will end when the last patient has completed ~18 months of safety follow-up from the last dose of blinded obinutuzumab infusion.*

*Patients who receive additional therapies that reduce peripheral B-cell counts will not be included in BCFU.*

### **3.3 RATIONALE FOR STUDY DESIGN**

#### **3.3.1 Rationale for Obinutuzumab Dose and Schedule**

The Phase II dose selection for obinutuzumab is based on experimental documentation of the drug's potency relative to rituximab in head-to-head in vitro nonclinical experiments and primate experiments and by partial efficacy demonstrated in the LUNAR study with rituximab. The most relevant in vitro experiments demonstrated a 5-to 50-fold greater ADCC potency for obinutuzumab in a Z138 lymphoma cell line experiment and in a nonclinical xenograft mouse tumor volume experiment (Mössner et al. 2010). A related primate study (Mössner et al. 2010) evaluated the depletion of B cells in cynomolgous monkeys evaluating rituximab at  $2 \times 10$  mg/kg versus obinutuzumab at  $2 \times 10$  mg/kg and at  $2 \times 30$  mg/kg. This controlled experiment demonstrated a significantly greater B-cell depletion (CD40+CD21+) with obinutuzumab versus rituximab at the  $2 \times 10$  mg/kg dose level in lymph nodes and splenic tissue, and no significant difference in depletion between the two obinutuzumab doses.

Glycoengineered modifications resulting in significantly higher ADCC and the direct type II cell-killing mechanism translate into results from mouse and primate experiments that confirm greater potency for obinutuzumab. These findings were confirmed in the CLL11 Stage 2 head-to-head study of obinutuzumab versus rituximab (Goede et al. 2014), which demonstrated greater progression-free survival and also greater minimal residual disease negativity for obinutuzumab even in protected micro-environments such as the bone marrow.

In the LUNAR study, rituximab was dosed at 1000 mg on Days 1, 15, 168, and 182 with a PD goal of peripheral blood CD19+ B-cell depletion by use of normal sensitivity flow cytometry up to and including Week 52, the primary endpoint of the study. This dosing schema may not have accomplished the PD goal of B-cell depletion in the kidney, and the degree of B-cell depletion in the kidney remains unknown since routine renal

biopsies are not part of clinical practice and there are no existing blood or urine biomarkers capable of evaluating this question. For these reasons, obinutuzumab will be studied at a comparable dose (1000 mg) and comparable interval (on Days 1, 15, 168, and 182) to assess whether the achieved CRR differs from the CRR rate observed in the LUNAR Study.

### **3.3.2 Rationale for Patient Population**

The population to be enrolled in this protocol will be patients with ISN/RPS Class III or IV LN with active inflammatory processes as evidenced by a renal biopsy within 6 months of screening or during screening and elevated proteinuria. Class III and IV LN was selected because these patients have proliferative disease, which has a poor prognosis and requires significant immunosuppressive therapy. Patients with Class V membranous nephritis will be allowed protocol entry if the Class V membranous nephritis is detected on a renal biopsy and concurrent with Class III or IV disease. Patients entering the protocol may have either relapsing or newly diagnosed disease. The population selected for this study has the highest unmet medical needs, and prior data suggesting partial responses in this population with anti-CD20 mAbs rituximab and ocrelizumab suggest that enrollment is feasible and that a greater response may be achieved with the more potent drug obinutuzumab.

### **3.3.3 Rationale for Control Group**

Study WA29748 will be a placebo-controlled study provided on top of background immunosuppression with MMF. Add-on study designs are appropriate in this population, and the provision of no background immunosuppression in a placebo-controlled study would represent inadequate therapy for a population at risk for severe renal damage.

### **3.3.4 Rationale for Biomarker Assessments**

The variability in response to previous B-cell targeting therapies in LN is incompletely understood. This variability may reflect the heterogeneity of this disease as it relates to varying degrees of B-cell involvement among patients, but it may also point to incomplete B-cell depletion. Predictive and PD biomarkers have the potential to differentiate between these possible explanations and will be collected in this study to improve understanding of any variability seen for clinical outcome to obinutuzumab treatment. Predictive biomarker samples will be collected prior to dosing in an effort to identify those patients with B-cell driven pathogenesis who are most likely to respond to obinutuzumab. PD biomarker assessment will evaluate the modulation of B-cell numbers and activity by obinutuzumab, and may additionally inform PK/PD modeling to support the dose and dose regimen. As these biomarkers may also have prognostic value, their association with disease progression will also be explored.

## 3.4 OUTCOME MEASURES

### 3.4.1 Efficacy 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:

- 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  $< 0.5$

#### 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  $\leq 3.0$ , 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 creatinine as evidenced by serum creatinine  $\leq$  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.

### **3.4.2 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*

### **3.4.3 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

### **3.4.4 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 (AUC) and maximum concentration observed ( $C_{max}$ ) 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.

### **3.4.5 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.

### **3.4.6 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 (SLEDAI)-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

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 examine the biopsy sample for routine histology to enable clinical decisions but should not review immunohistopathology results that evaluate the presence or absence of B cells or be informed of their results.

It is important to ensure that patients' renal biopsy samples are classified in a consistent manner. As with other quantitative histopathology procedures, there can be significant inter-personal variation in the scoring of renal biopsy samples. Therefore, the biopsy sample used for entry qualification will be collected (where possible) and sent for reading at a specialist review laboratory before being returned to the study site. This will allow accurate analysis and will enhance the scientific credibility of the study. Determination of eligibility, however, will be made based on the local renal biopsy review.

The original microscopic sections from each patient's biopsy sample will be re-read by a panel of renal histopathologists. Additional slides for investigating disease characteristics are also requested as described in the Laboratory Manual. The biopsy consensus evaluation process will be as follows:

- A panel of independent nephro-pathologists will be used for the study.
- A consensus reading of each renal biopsy will be made by two of the pathologists.
- Discrepancies will be resolved at periodic consensus meetings.

However, reading at the specialist review laboratory is not required prior to study entry. Any subsequent biopsies (i.e., following treatment) will also undergo the same analysis

at the specialist review laboratory. Lack of availability of a biopsy sample specimen will not preclude enrollment in the study, as long as the pathology report confirming eligibility is available. Follow-up repeat biopsies may be performed as clinically required by the investigator and also provided for analysis by the centralized facility.

All repeat biopsy samples will be read with a central reading methodology. The baseline biopsy sample that was used to determine the eligibility of the patient will be sent to the central reading site, as this will allow comparison between pre- and post-treatment samples. An operational manual that outlines processes for the acquisition of renal biopsy data will be implemented as part of this protocol.

## **4. MATERIALS AND METHODS**

### **4.1 PATIENTS**

All patients will be screened for conformance with the following inclusion and exclusion criteria. 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.

#### **4.1.1 Inclusion Criteria**

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age 18–75 years
- Ability to comply with the study protocol, in the investigator's judgment
- Diagnosis of SLE, according to current ACR criteria (at least four criteria must be present, one of which must be a positive ANA)
- 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.
- Proteinuria (urine protein to creatinine ratio) > 1.0, based on a 24-hour urine collection
- 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.

- 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.

#### **4.1.2 Exclusion Criteria**

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

- 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
- Presence of rapidly progressive glomerulonephritis defined by
  - The presence of crescent formation in ≥ 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.
- Severe renal impairment as defined by estimated GFR < 30 mL/min or the need for dialysis or renal transplant
- Greater than 50% of glomeruli with sclerosis on renal biopsy
- Treatment with cyclophosphamide or calcineurin inhibitors within the 3 months prior to randomization
- 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
- Lack of peripheral venous access
- Pregnancy or lactation
- History of severe allergic or anaphylactic reactions to mAbs or known hypersensitivity to any component of the obinutuzumab infusion

- 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
- 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
- Known HIV infection
- 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
- History of serious recurrent or chronic infection
- 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)
- Currently active alcohol or drug abuse or history of alcohol or drug abuse within 52 weeks prior to screening
- Major surgery requiring hospitalization within 4 weeks of randomization (excluding diagnostic surgery)
- Previous treatment with an anti-CD20–targeted therapy within 12 months of randomization
- Previous treatment with a biologic B-cell–targeted therapy (other than anti-CD20) within 6 months of randomization
- Treatment with any investigational agent within 28 days of randomization or five halflives of the investigational drug (whichever is longer)
- Receipt of a live vaccine within 28 days prior to screening
- Intolerance or contraindication to oral or IV corticosteroids
- Aspartate aminotransferase or alanine aminotransferase  $>2.5 \times$  ULN
- Amylase or lipase  $>2 \times$  ULN
- Neutrophils  $<1.5 \times 10^3/\mu\text{L}$
- Positive hepatitis B surface antigen (HbSAg) or hepatitis C serology. Patients who are HBsAg negative and hepatitis B core antibody (HBcAb) positive with no detectable DNA will be allowed into the study but will require regular monitoring of hepatitis B virus (HBV) DNA.
- Hemoglobin  $<7 \text{ g/dL}$ , unless caused by autoimmune hemolytic anemia resulting from SLE
- Platelet count  $<10,000/\mu\text{L}$
- Positive serum human chorionic gonadotropin measured prior to the first obinutuzumab infusion
- Known intolerance to MMF and MPA

## **4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING**

The investigator or the investigator's research staff will provide patient eligibility information through the interactive voice/Web response system (IxRS) at randomization. Each patient will be randomized and assigned a unique identification number. As confirmation, the investigator will be provided with written verification of each patient's registration.

Patients will be randomized to receive obinutuzumab or placebo in a 1:1 ratio.

The randomization of patients into treatment and control groups will be managed by a central IxRS vendor by use of a block design. The factors for balancing between the treatment groups will be the following:

- Treatment balance within each race stratum for the following:
  - Region (Afro Caribbean/African American versus others)
  - United States versus non-U.S. sites

Because it is important to maintain blinding to preserve the integrity of the data collected, all laboratory studies of blood specimens, with unblinding potential, will be performed by a central laboratory. Therefore, site personnel and the Sponsor's staff involved with the conduct of the study will not receive unblinded data related to peripheral B-cell counts, PK results, specific immunoglobulin levels, or ADA results during the study, as listed below, until all eligible patients have completed their Week 52 visit.

While PK samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK assay results for these patients are generally not needed for the safe conduct or proper interpretation of this study. Sponsor personnel responsible for performing PK assays will be unblinded to patients' treatment assignments to identify appropriate PK samples to be analyzed. Samples from patients who are assigned to the comparator arm will not be analyzed except by request (e.g., to evaluate a possible error in dosing).

If unblinding is necessary for patient management (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. Treatment codes should not be broken except in emergency situations. If the investigator wishes to know the identity of the study treatment for any other reason, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event).

For regulatory reporting purposes and if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected suspected adverse reactions

(see Section 5.7) that are considered by the investigator or Sponsor to be related to the study drug.

#### **4.3 STUDY TREATMENT**

##### **4.3.1 Formulation, Packaging, and Handling**

###### **4.3.1.1 Obinutuzumab and Placebo**

Obinutuzumab is provided as a single-dose, sterile liquid formulation in a 50-mL pharmaceutical grade glass vial containing a nominal 1000 mg of obinutuzumab (G3 material). The formulated drug product consists of 25 mg/mL drug substance (G3) formulated in histidine, trehalose, and poloxamer 188. The vials contain 41 mL (with 2.5% overfill).

###### **Handling and Storage**

The recommended storage conditions for the obinutuzumab drug product are between 2°C and 8°C and protected from light. Chemical and physical in-use stability for obinutuzumab dilutions in 0.9% sodium chloride (NaCl) have been demonstrated for 24 hours at 2°C–8°C and at ambient temperature and ambient room lighting.

The prepared diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C–8°C. Obinutuzumab should not be frozen or shaken. It should be mixed gently. All transfer procedures require strict adherence to aseptic techniques. An additional in-line filter should not be used because of potential adsorption.

For further details see the Obinutuzumab Investigator's Brochure, pharmacy manual, and local prescribing information.

The placebo employed in this study will be a generic placebo of normal saline, and the double-blinded format will utilize an unblinded pharmacist to enable delivery of obinutuzumab and obinutuzumab placebo.

###### **4.3.1.2 Methylprednisolone and Placebo**

Methylprednisolone and methylprednisolone placebo may be reimbursed by the Sponsor as per local requirements. Local supply of commercially available stock should be used or matching saline solution – prepared by the unblinded pharmacist to maintain the double blind status of the study. For information on the formulation and handling of methylprednisolone, see the pharmacy manual and the local prescribing information for methylprednisolone.

###### **4.3.1.3 Mycophenolate Mofetil/Mycophenolic Acid**

For information on the formulation of and the packaging and handling requirements for MMF and MPA, see the local prescribing information.

#### **4.3.2 Dosage, Administration, and Compliance**

##### **4.3.2.1 Obinutuzumab and Placebo**

Obinutuzumab will be administered by IV infusion at a dose of 1000 mg on Days 1, 15, 168, and 182.

Obinutuzumab must be administered in a hospital or clinic environment where full resuscitation facilities are immediately available and under close supervision of the investigator or designee. Although study drug may be administered on an outpatient basis, patients may be hospitalized for observation at the discretion of the investigator.

See the Obinutuzumab Administration section below for detailed study drug administration instructions for the first infusions (Day 1) and subsequent infusions (Day 15, Day 168, and Day 182) of the two dosing intervals.

Obinutuzumab vials are biologically and chemically stable at 2°C–8°C (36°F–46°F). Do not use beyond the expiration date stamped on the carton. Obinutuzumab should be protected from direct sunlight.

For further details, see the immunology Obinutuzumab Investigator's Brochure and the local prescribing information.

#### **Obinutuzumab Dose and Schedule**

Obinutuzumab will be administered by IV infusion as an absolute (flat) dose of 1000 mg for four infusions on Days 1, 15, 168, and 182. Placebo infusion will be infused in the same volume and on the same scheduled days in the control arm.

#### **Obinutuzumab Preparation**

Obinutuzumab drug product that is intended for IV infusion is prepared by dilution of the drug product into an infusion bag containing 0.9% NaCl to the final drug concentration of 4 mg/mL. Using a 250-mL infusion bag containing 0.9% NaCl, withdraw and discard 40 mL of the NaCl. Withdraw 40 mL of obinutuzumab from a single glass vial and inject it into the infusion bag (discard any unused portion of obinutuzumab remaining in the vial). Gently invert the infusion bag to mix the solution; do not shake.

Administration sets with polyvinyl chloride, polyurethane, or polyethylene as product contact surface and IV bags with polyolefin, polypropylene, polyvinyl chloride, or polyethylene as product contact surface are compatible and may be used. Use of a port or a peripherally inserted central catheter (PICC line) is acceptable.

Do not use obinutuzumab beyond the expiration date stamped on the carton.

#### **Obinutuzumab Administration**

Obinutuzumab should be administered to patients in a clinical setting (inpatient or outpatient) where full emergency resuscitation facilities are immediately available and patients should be under close supervision of the investigator at all times. Do not

administer as an IV push or bolus. After the end of the first infusion, the IV line should remain in place for  $\geq$  2 hours in order to be able to administer IV drugs if necessary. If no adverse events occur after 2 hours, 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.

Patients should receive prophylactic treatment with acetaminophen (650–1000 mg) and diphenhydramine (50 mg; or equivalent dose of a similar agent) by mouth 30–60 minutes prior to the study drug infusion. Methylprednisolone 80 mg IV must be given 30–60 minutes prior to the start of infusions on Days 1, 15, 168, and 182.

Patients who are administered an antihistamine (e.g., diphenhydramine) for the treatment or prevention of IRRs should be given appropriate warnings prior to the patients' discharge about drowsiness and impairment of ability to drive.

Instructions for administration of obinutuzumab infusions are provided in [Table 2](#) and [Appendix 7](#).

**Table 2 Administration of Obinutuzumab Infusions**

First Infusion (Day 1)	Subsequent Infusions (Days 15, 168, and 182)
Begin infusion at an initial rate of 50 mg/hr. If no infusion reaction occurs, increase the infusion rate in 50-mg/hr increments every 30 minutes to a maximum of 400 mg/hr. If an infusion reaction develops, stop or slow the infusion. Administer infusion-reaction medications and supportive care in accordance with institutional protocol. Resume the infusion at a 50% reduction in rate (the rate being used at the time that the hypersensitivity or IRR occurred) if the reaction has resolved.	If a patient experienced an infusion reaction during the prior infusion, start at the same rate as the first infusion (50 mg/hr) and follow those directions as noted. If the patient tolerated the prior infusion well, begin infusion at a rate of 100 mg/hr. If no infusion reaction occurs, increase the infusion rate in 100-mg/hr increments every 30 minutes to a maximum of 400 mg/hr. If an infusion reaction develops, stop or slow the infusion. Administer infusion-reaction medications and supportive care in accordance with institutional protocol. Resume the infusion at a 50% reduction in rate (the rate being used at the time that the hypersensitivity or IRR occurred) if the reaction has resolved.

IRR=infusion-related reaction.

**Table 3 Management of Infusion-Related Reactions**

Infusion-Related Symptoms <sup>a</sup> Grade	Guidance
1–2	Slow or hold infusion. Give supportive treatment <sup>b</sup> . Upon symptom resolution, may resume infusion rate escalation at the investigator's discretion <sup>c</sup> .
3	Discontinue infusion. Give supportive treatment <sup>b</sup> . Upon symptom resolution, may resume infusion rate escalation, at investigator discretion <sup>c</sup> . Note: If the same adverse event recurs with the same severity, treatment must be permanently discontinued.
4	Discontinue infusion immediately, treat symptoms aggressively, and do not restart drug.

IV=intravenous.

Note: These recommendations do not address life-threatening events, including anaphylaxis, for which all appropriate standard measures (including full resuscitation medications and equipment) must be available and should be used as clinically indicated. For further details see Section 5.1.1.

<sup>a</sup> Refer to National Cancer Institute Common Terminology Criteria for Adverse Events, v4.0, for the grading of symptoms. This table does not refer to management of immunoglobulin E-mediated allergic reactions.

<sup>b</sup> Supportive treatment: Patients should be treated with acetaminophen/paracetamol and an antihistamine such as diphenhydramine if they have not been received in the last 4 hours. IV saline may be indicated. For bronchospasm, urticaria, or dyspnea, patients may require antihistamines, oxygen, corticosteroids (e.g., 100 mg of IV prednisolone or equivalent), and/or bronchodilators. For hypotension, patients may require vasopressors.

<sup>c</sup> Infusion rate escalation after re-initiation: Upon complete resolution of symptoms, the infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion-related symptoms, the rate of infusion may be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.

#### **4.3.2.2 Mycophenolate Mofetil/Mycophenolic Acid**

All patients will either continue on or initiate use of MMF (or MPA) during screening or no later than Day 1. The initial dosage will be 1500 mg/day by mouth (or equivalent), given in two or three divided doses and titrated upward to 2.0–2.5 g/day (or equivalent) in divided doses by Week 4. The dose may be increased by 500 mg/wk (or equivalent), as tolerated up to a maximum dosage of 2.5 g/day (or equivalent). Reductions, as outlined in [Appendix 4](#), will be allowed because of adverse effects. Investigators, at their discretion, may use MPA as a substitute for MMF, with a 360-mg dose being equivalent to a 500-mg dose of MMF.

Based on randomized controlled clinical studies, approximately 30–40% of patients with LN may achieve a CRR with initial therapy with either cyclophosphamide or MMF in combination with corticosteroids (Dall'Era et al. 2011). In this group, the benefit of added therapy may be minimal, and the risks of added therapy may be unwarranted. The investigator should assess whether eligible patients may benefit from an initial trial of standard-of-care therapy prior to enrollment into the study.

For those patients who enter the study already receiving a dosage of MMF (or MPA) higher than 1500 mg/day (or equivalent), MMF (or MPA) will be titrated upward, as tolerated, to a goal of 2.5 g/day (or equivalent), given in divided doses, by Week 4. A patient's current dose of MMF (or equivalent) will be given in two or three divided doses and will be increased by 500 mg/wk (or equivalent) as tolerated. Refer to [Appendix 4](#) for further details.

Use of MMF (or equivalent) during pregnancy is associated with increased risks of spontaneous abortion and congenital malformations, especially external ear and other facial abnormalities, including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, kidney, and nervous system. Because of this, women of reproductive potential must be counseled regarding pregnancy prevention and planning and must use effective contraception prior to initiation of this therapy.

Because MMF (or equivalent) may have an interaction with oral contraceptives that could theoretically decrease its effectiveness, if patients (or partners of patients) enrolling in this study use hormonal contraceptives as their primary method of contraception, these must be supplemented by either a barrier method of contraception or an intra-uterine contraceptive device (see Section [4.1.1](#), and MMF/MPA U.S. Package Insert).

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section [5.1](#).

Any overdose or incorrect administration of MMF (or equivalent) should be noted on the MMF/MPA Administration electronic case report form (eCRF). Adverse events associated with an overdose or incorrect administration of MMF/MPA should be recorded on the Adverse Event eCRF.

#### **4.3.2.3 Corticosteroid Administration Initial Study Corticosteroid Dose**

All patients will receive a combination of IV and oral corticosteroids as part of their initial therapy for LN. Methylprednisolone (Solu-Medrol) will be implemented in this protocol for two purposes: as part of the usual care for patients with active Class III or IV LN and also to reduce IRRs on the days of obinutuzumab/placebo infusions. Up to three doses of IV methylprednisolone 1000 mg will be given on the basis of investigator judgment and local practice. Up to three 1000 mg infusions may have been initiated prior to

screening or during the screening interval, and proper documentation of the number and date of infusions must occur.

On Days 1, 15, 168, and 182, patients will receive 80mg IV methylprednisolone or placebo 30–60 minutes prior to study drug infusion to prevent IRRs.

Additionally, oral prednisone may be initiated before or during the screening interval, and a taper will commence on Day 16 of the protocol. From Days 2 to 16, 0.50 mg/kg/day oral prednisone will be given (maximum dose of 60 mg), except on the day of IV methylprednisolone/placebo infusions, and will continue until Day 16. From Day 16 onward, a prednisone taper will commence as directed in [Appendix 5](#). See [Appendix 8](#) for list of corticosteroid equivalence.

### **Corticosteroid Taper**

All patients will undergo a scheduled corticosteroid taper commencing on Day 16. Patients will fractionally reduce their prednisone dose over 10 weeks until the dose is 7.5 mg/day by Week 12 (see [Appendix 5](#)). Deviations from the scheduled primary prednisone taper for any reason other than SLE disease activity will confound interpretation, so every attempt should be made to adhere to the tapering schedule. After the 10 weeks of tapering, patients will continue on prednisone at 7.5 mg/day. In patients whose disease is too clinically active for the patient to make the first step in their prednisone taper, as evidenced by active urinary sediment, rising serum creatinine, or moderate-to-severe extrarenal symptoms, these patients may continue to receive their initial prednisone dose for up to an additional 28 days. Patients who have started their taper and whose disease is too clinically active to continue tapering, may, using the same criteria as above, remain at the taper dose achieved for up to an additional 28 days. The prednisone dose may not be increased beyond the taper dose achieved. Patients will be discouraged from making adjustments to their prednisone dose and should contact the investigator and be examined before altering the prednisone taper so that deviations from the schedule can be justified and its relationship to lupus activity can be ascertained.

After patients complete their Week 52 visit, investigators at their discretion may taper the oral prednisone further, if they believe it is clinically warranted.

### **Corticosteroid Dosing for Renal Flares**

To maintain consistency in the treatment of renal flares, retreatment with higher doses of corticosteroids is permitted if judged clinically appropriate by the investigator and if patients meet criteria for a renal flare (see [Appendix 5](#)). Patients may be treated with prednisone (up to 0.5 mg/kg; not to exceed 60 mg/day) for 2 weeks. Prednisone will then be tapered to achieve 10 mg/day within 6 weeks after the initial corticosteroid increase and may further be tapered to 7.5 mg/day at the discretion of the investigator. Patients who do not exhibit a response to the initial 2-week course of increased corticosteroids and who initiate a new immunosuppressive therapy will be deemed

treatment failures and will continue regular visits and will not receive additional study drug.

### **Corticosteroid Dose Increases Due to Extrarenal Disease Flare**

Patients will be allowed to receive corticosteroids for emergent illness (trauma, severe asthma) or surgery, if clinically warranted; the corticosteroid use should be limited to a total of  $\leq 7$  days, if possible. Investigators will be allowed to increase the prednisone dose by  $\leq 2.5$  mg/day to treat symptoms of adrenal insufficiency or corticosteroid withdrawal.

Patients who experience a severe extrarenal SLE flare may receive treatment with additional oral corticosteroids, if judged clinically appropriate by the investigator (see [Appendix 5](#)). These patients may be retreated with prednisone (up to 1.0 mg/kg) for up to 2 weeks on the basis of the severity of disease and organ system involvement and the dosage should be tapered to 7.5 mg/day, following a separate tapering schedule as listed in [Appendix 5](#). Patients experiencing a mild or moderate extrarenal flare may temporarily increase their prednisone dose by up to 20 mg per day and taper this dose over 4 weeks, if judged clinically appropriate by the investigator. IV corticosteroids in equivalent doses are allowed if gastrointestinal (GI) involvement temporarily precludes treatment with oral corticosteroids. Patients who do not show improvement in their symptoms after 2 weeks of increased corticosteroid treatment are considered to be nonresponsive to corticosteroids. Efforts should be made to reduce corticosteroid exposure to the minimally effective level to reduce corticosteroid-associated toxicity.

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 overdose or incorrect administration of prednisone or methylprednisolone should be noted on the Corticosteroid Administration eCRF. Adverse events associated with an overdose or incorrect administration of corticosteroids should be recorded on the Adverse Event eCRF.

#### **4.3.3 Dosage Modification**

Dose modification is not permitted during this study; however, the rate of infusion may be adjusted in the event of an IRR.

If a patient experiences an IRR that requires interruption of the infusion and the investigator determines it should not be restarted, the patient should continue to be followed in the study for safety.

#### **4.3.4        Investigational Medicinal Product Accountability**

Obinutuzumab will be provided by the Sponsor. The study site will acknowledge receipt of investigational medicinal products (IMPs) using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. Study sites will maintain adequate records for receipt and disposition of study drug and maintain adequate drug dispensing and return records for monitor inspection.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

#### **4.3.5        Post-Study Access to Obinutuzumab**

The Sponsor will offer post-study access to the study drug, obinutuzumab, free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive study drug after completing the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for LN.
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for LN.
- Provision of study drug is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

[http://www.roche.com/policy\\_continued\\_access\\_to\\_investigational\\_medicines.pdf](http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf)

## **4.4 CONCOMITANT THERAPY**

### **4.4.1 Permitted Therapy**

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to screening to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

#### **4.4.1.1 Other Concomitant Therapy**

##### **Antimalarial Medications**

Antimalarial medications may influence the development of subsequent lupus flares (Canadian Hydroxychloroquine Study Group 1991). Patients taking antimalarial medications at study entry should maintain a constant dosage throughout the study. Patients not previously on antimalarial medications may be enrolled in the study but should not initiate antimalarial medications unless experiencing a disease flare that is unresponsive to corticosteroids. [Table 4](#) lists the antimalarial medications and dose ranges expected to be used during the course of the study.

**Table 4 Antimalarial Medications**

Antimalarial Medication	Dose Range (Oral)
Hydroxychloroquine	200–400 mg daily
Chloroquine	500 mg every day or every other day
Quinacrine	100 mg every day

##### **Antihypertensive Therapy**

All patients who are not currently taking either an ACE inhibitor or an angiotensin-receptor blocker (ARB) should be started on one at screening. Patients should be on either an ACE inhibitor or ARB for at least 10 days prior to randomization. Combination therapy with the two agents will not be allowed.

During screening, every effort should be made to adequately control patients' blood pressures. The dose of the ACE inhibitor or ARB may be titrated upward to the maximum recommended dose in the current package insert to achieve adequate blood pressure control as recommended by the Eighth Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (James et al. 2014). If adequate blood pressure control is not achieved, patients may be started on additional antihypertensive agents but not on agents that affect proteinuria

(e.g., nondihydropyridine calcium channel blockers, aldosterone antagonists, direct renin antagonists). Additional agents that specifically target the renin-angiotensin system cannot be initiated during the study. Suggested dose ranges for specific ACE inhibitors and ARBs are listed in [Table 5](#).

ACE inhibitor and ARB therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension and hyperkalemia). The use of ACE inhibitors and ARBs is not recommended during the first trimester of pregnancy and is contra-indicated during the 2nd and 3rd trimester of pregnancy.

If patients are intolerant to ACE inhibitors and ARBs, they may use either a direct renin inhibitor or aldosterone antagonists, but not in combination.

**Table 5 Suggested Dose Ranges for Angiotensin-Converting Enzyme Inhibitors and Angiotensin-Receptor Blockers**

ACE Inhibitor or ARB	Dose Range (Oral) (mg/day)
ACE inhibitors	
Benazepril	10–80
Ramipril	2.5–10
Lisinopril	10–80
Enalapril	10–40
Quinapril	10–80
Captopril	75–450
Perindopril	4–16
Trandolapril	1–8
Moexipril	7.5–30
ARBs	
Eprosartan	400–600
Valsartan	80–320
Olmesartan	20–40
Candesartan	8–32
Telmisartan	20–80
Losartan	25–100
Irbesartan	75–300

ACE=angiotensin-converting enzyme;

ARB=Angiotensin-Receptor Blockers.

## **Vitamins and Supplements**

Patients who are not already taking vitamin D (800 IU/day) and calcium supplements (1200 mg/day calcium citrate or 1500 mg/day calcium carbonate) should start taking these supplements during screening. Investigators should follow current ACR guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis (ACR 2001) or, for female patients in Canada >50 years of age, Canadian guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis (Cheung et al. 2004).

### **4.4.1.2 Withdrawal of Immunosuppression after Week 52**

Patients who enter the Study Extension Period at Week 52 will remain on background standard-of-care immunosuppressant treatment until they have maintained their best achieved response, which must be at least an adequate clinical benefit for at least 6 months. After Week 52, the investigator may elect to continue MMF at a reduced dose or switch the patient to receive azathioprine at 2mg/kg/day on the basis of local practice. If this response is achieved and the patient's condition is considered to be stable, an attempt may be made to reduce or discontinue immunosuppressive treatment while closely monitoring renal parameters.

The following reduction strategy is recommended:

Azathioprine: Reduce by 50 mg/day every 4 weeks.

MMF (or equivalent): Reduce by 500 mg/day (or equivalent) every 4 weeks.

Patients whose conditions deteriorate on withdrawal of background therapy in this phase may receive re-induction therapy, which can include high-dose corticosteroids, immunosuppressant treatment such as MMF/MPA or obinutuzumab, or a combination of these as considered appropriate by the investigator.

After Week 52, any treatment changes are entirely at the discretion of the investigator.

### **4.4.2 Concomitant Therapy and Clinical Practice**

Concomitant medications such as HMG-coA-reductase inhibitors and bisphosphonates will be recorded but not initiated during the study unless considered clinically indicated by the treating investigator after discussion with the Medical Monitor. If patients enter the study taking these medications, every effort will be made to keep their dosage stable to prevent confounding of study results.

### **4.4.3 Immunization during Peripheral B-Cell Depletion**

The efficacy and safety of immunization during periods of peripheral B-cell depletion have not been adequately studied. It is recommended that a patient's vaccination record and the need for immunization be carefully evaluated prior to receiving study drug. For patients who are likely to require immunization in the foreseeable future, such as patients planning to travel to countries where specific immunization is required or patients requiring a vaccination/booster for their professional activity, any required

vaccination/booster must be given at least 28 days prior to randomization. Review of a patient's immunization status or need for the following vaccinations in advance of randomization is recommended: tetanus; diphtheria; influenza; pneumococcus polysaccharide; *Varicella*; measles, mumps, and rubella (MMR); and hepatitis B vaccines.

The safety and efficacy of immunization with a live or attenuated live vaccine in B cell-depleted patients are not known. For this reason, the use of live or attenuated vaccines (e.g., measles, mumps, rubella, oral polio vaccine, *Bacillus Calmette-Guérin* [BCG], typhoid, yellow fever, vaccinia, or any other vaccines not yet licensed but belonging to this category) is specifically excluded for 28 days prior to screening through the end of study participation.

Vaccines that do not contain live organisms (e.g., influenza, Pneumovax<sup>®</sup>, tetanus) are not prohibited; however, vaccines received during peripheral B-cell depletion may be ineffective.

#### **4.4.4 Prohibited Therapy**

Use of the following therapies is prohibited during the study:

- Investigational therapies from within 28 days or 5 half-lives of randomization (whichever is longer) and throughout the study
- Exposure to an anti-CD20 targeted biologic therapy from the 12 months prior to randomization and throughout the study
- Treatment with a biologic B-cell-targeted therapy other than anti-CD20 within 6 months of randomization and throughout the study
- Live virus vaccines from 28 days before the screening visit and throughout the study
- NSAIDs, calcineurin inhibitors, or other nephrotoxic drugs during the study conduct

The use of NSAIDs, with the exception of aspirin when used for cardiovascular protection, is prohibited in this study, given the potential effect of NSAIDs on renal function and proteinuria. If patients are taking NSAIDs prior to enrollment, these medications must be discontinued during screening (at least 5 half-lives prior to randomization). If the investigator believes that it is necessary to prescribe NSAIDs for a patient during the study, he or she should inform the Medical Monitor, and every attempt should be made to limit the use of NSAID treatment. If used, the use of NSAIDs and other symptomatic medications that are both prescribed and available over the counter will be recorded at each visit. Patients will be asked by the investigator whether these medications were used for a SLE-related symptom (e.g., pericarditis) or for symptoms not attributed to lupus (e.g., menstrual discomfort).

Other immunosuppressive agents not specifically allowed in the study as described above will not be allowed during the study and must be discontinued during the

screening period when patients become eligible for study participation and fulfill exclusion criteria.

## **4.5 STUDY ASSESSMENTS**

See [Appendix 1](#) for the schedule of assessments performed during the study.

### **4.5.1 Informed Consent Forms and Screening Log**

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

### **4.5.2 Medical History and Demographic Data**

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the screening visit.

Demographic data will include age, sex, and self-reported race/ethnicity. The collection of information on race is important in the context of this protocol because multiple studies have confirmed that patients with an African descent tend to have the worst prognosis for renal function. For this reason, African heritage will be a stratification variable.

### **4.5.3 Physical Examinations**

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, GI, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

A chest x-ray, if not done within 3 months prior to screening, will also be done at screening.

#### **4.5.4 Vital Signs**

Vital signs will include measurements of respiratory rate, body temperature, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position for 5 minutes. The same arm for blood pressure measurements should be used consistently throughout the study, if possible.

#### **4.5.5 Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) Assessment**

The SLEDAI-2K instrument (see [Appendix 13](#)) will be employed in this study to assess, at baseline, the occurrence of organ involvement other than the kidney. It will be employed at regular visits and at unscheduled visits to capture changes in lupus-related disease activity after randomization. The SLEDAI-2K instrument was selected for its ease of use, validation, and employment in the BELONG study. SLEDAI-2K is assessed for the 10 days prior to the patient's visit and has 24 items and a total score of 105.

#### **4.5.6 Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage Index for Systemic Lupus Erythematosus**

The Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index for SLE (see [Appendix 10](#)) will be utilized to assess organ damage as opposed to the collection of disease activity. Damage is defined as non-reversible change not related to active inflammation.

#### **4.5.7 Glucocorticoid Toxicity Change Index**

The GTCI is an exploratory standardized measure of damage related to use of glucocorticoids (see [Appendix 14](#)). The GTCI will be incorporated into this study to better quantify the accrual of damage linked to corticosteroid use in patients with LN and may allow for an improved understanding of standard of care and patient phenotype.

#### **4.5.8 Laboratory, Biomarker, and Other Biological Samples**

The following laboratory tests will be recorded at the timepoints indicated in the Schedule of Assessments (see [Appendix 1](#)). It is required that sample specimens be sent to the central laboratory at all study timepoints, with the exception of urinalysis and hematology samples collected for safety monitoring of MMF. Full details of the sample handling can be found in the Laboratory Manual.

The full laboratory assessments that will be assessed according to the study schedule of assessments are described below:

- Hematology: To include CBC, hemoglobin, hematocrit, RBC, mean corpuscular volume, mean corpuscular hemoglobin, WBC (absolute and differential), and quantitative platelet count. If a test is required to assess hemolytic anemia, it will be performed locally.

- Blood chemistry: AST/SGOT, ALT/SGPT, alkaline phosphatase, amylase, lipase, total protein, albumin, cholesterol, total bilirubin, urea, uric acid, creatinine, random glucose, potassium, sodium, chloride, calcium, phosphorus, lactic dehydrogenase, CPK and triglycerides.
- Urinalysis: Including dipstick for blood, nitrite, protein, and glucose and urine microscopy. Preferably, urinary protein to creatinine ratio should be performed on a first morning urine sample (see [Appendix 9](#))
- 24-hour urine collection: To be analyzed for total protein, total creatinine, creatinine clearance, and protein to creatinine ratio. To be performed at screening, randomization, and at Months 3, 6, 9, and 12.
- Flow cytometry: B cell (including CD19, CD27, CD38, and IgD), T cell (CD3, 4, 8) and NK cells (CD16, CD56). Flow cytometry results will remain blinded until the study is unblinded.
- Autoantibody profile: To include ANA, anti-dsDNA, anti-Sm, anti-RNP, anti-Ro, antiLa, anti-C1q.
- Anti-ds-DNA antibody: To be measured by ELISA at all visits as part of SLEDAI2K assessment
- Quantitative immunoglobulin: Total Ig levels including IgG, IgM, and IgA isotypes
- Complement: Including C3, C4, and CH50
- Antibody titers: Measurement of antibody titers to common antigens (mumps, Varicella, rubella, tetanus, influenza, and *S. pneumoniae*) will be performed according to the schedule of assessments. This information is used to assess the effect of obinutuzumab on specific humoral immunity to bacterial and viral antigens.
- Viral hepatitis: Measurement of HBsAg, HBcAb, and hepatitis C antibody. Patients who are HBsAg negative and HBcAb positive will also be evaluated for HBV DNA.
- Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation) will have a pregnancy test at each visit. Positive test results will be confirmed with a serum pregnancy test. The infusion must not be administered unless the pregnancy test is negative.
- Pharmacokinetics and ADA: To be measured as outlined in the schedule of assessments.

The following samples will be sent to the Sponsor or a designee for analysis:

- Cells from blood and urine for B-cell and lupus-related biomarkers, which may include but are not restricted to CD19+ B cells and mRNA associated with B-cell activity
- Serum, plasma, and urine for B-cell and lupus-related biomarkers, which may include but are not restricted to B-cell activating factor (BAFF)
- Renal biopsy slides and/or formalin-fixed paraffin-embedded blocks for immunohistopathology assessment

Any leftover material from pharmacokinetics, ADA, and biomarker samples may be used for additional assay development and assay validation purposes during the development of study- or compound-related assays and exploratory research in addition to the mentioned intended uses. These samples will be stored until the study results have been reported, with the exception of some blood, tissue, and urine samples that might be stored for 5 years after all study data have been collected. For patients who agree to take part in optional long-term storage at Roche Clinical Repository (RCR), unused blood, urine, and kidney biopsy samples will be stored and destroyed no later than 15 years after the date of final closure of the associated clinical database.

#### **4.5.9        Electrocardiograms**

Twelve lead ECGs should be taken at the timepoints indicated in the schedule of assessments. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

If, at a particular post-dose timepoint, the mean QTcF is  $>500$  ms and/or  $>60$  ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Section 5.1.9. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

Comments generated automatically by the ECG machine should not be recorded unless confirmed by a physician. An ECG is also required if the patient discontinues from the study.

#### **4.5.10      Patient- and Physician-Reported Outcomes**

The Subject's Global Assessment of Disease Activity is the patient's overall assessment of his or her current disease activity will be measured on a 100 mm horizontal VAS. The left-hand extreme of the line is described as "none" (symptom-free) and the right-hand extreme as "severe".

The Physician's Global Assessment of Disease Activity is the physician's overall assessment of the patient's current disease activity. It is measured on a 100 mm horizontal VAS. The left-hand extreme of the line is described as "none" (symptom-free) and the right-hand extreme as "severe".

#### **4.5.11      Samples for Roche Clinical Repository**

##### **4.5.11.1    Overview of the Roche Clinical Repository**

The RCR is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

##### **4.5.11.2    Approval by the Institutional Review Board or Ethics Committee**

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol (Section 4.5.11) will not be applicable at that site.

##### **4.5.11.3    Sample Collection**

The following samples will be collected for research purposes, including but not limited to research on dynamic (non-inherited) biomarkers:

- Serum, plasma, and urine samples for research purposes, which may include but are not limited to research on biomarkers related to CD20 depletion, LN, SLE, or other autoimmune disease/inflammatory disorder
- Whole blood PAXgene samples for RNA extraction for research purposes, which may include but are not limited to research on biomarkers related to CD20 depletion, LN, SLE, or other autoimmune disease/inflammatory disorder

- Tissue samples from kidney biopsies for research on candidate biomarkers, which may include but are not limited to research on biomarkers related to CD20 depletion, LN, SLE, or other autoimmune disease/inflammatory disorder

The following samples will be collected for research purposes, including but not limited to research on genetic (inherited) biomarkers related to obinutuzumab or LN:

- Whole blood samples for DNA extraction for research purposes, including but not limited to research on biomarkers related to CD20 depletion, LN, SLE, or other autoimmune disease/inflammatory disorder

For all samples, dates of consent and specimen collection should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

#### **4.5.11.4 Confidentiality**

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens and associated data. Upon receipt by the RCR, each specimen is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with RCR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless required by local law. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RCR data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

#### **4.5.11.5 Consent to Participate in the Roche Clinical Repository**

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RCR specimens.

Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

In the event of an RCR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RCR research.

#### **4.5.11.6 Withdrawal from the Roche Clinical Repository**

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if the study is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the study is closed. A patient's withdrawal from Study WA29748 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study WA29748.

#### **4.5.11.7 Monitoring and Oversight**

RCR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC

review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

## **4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION**

### **4.6.1 Patient Discontinuation**

Patients have the right to voluntarily withdraw from the study at any time for any reason. The primary (and very uncommon) reason for withdrawal from the study should be the patient's withdrawal of consent. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include but are not limited to the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance, defined as the inability to comply with protocol procedures despite repeated interaction with the Principal Investigator

If a patient wishes to withdraw from the study, a distinction should be made concerning withdrawal from experimental treatment and complete withdrawal from the study.

Patients wishing to withdraw from treatment should continue to receive efficacy and safety evaluations in the study. Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

Patients who meet any of these criteria 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.

### **4.6.2 Study Treatment Discontinuation**

Patients must discontinue study treatment but remain in the study if they experience any of the following:

- Pregnancy
- Grade 4 IRR—the patient should be withdrawn from study treatment immediately
- Recurrence of Grade 3 IRR at rechallenge
- Grade 3 or 4 neutropenia that does not resolve to Grade  $\leq 2$  within 8 weeks
- Thrombocytopenia that does not resolve to Grade  $\leq 2$  within 8 weeks
- Hepatitis B reactivation despite the initiation of the appropriate anti-viral therapy

- Receipt of rescue cyto-toxic therapy, including cyclophosphamide, an anti-CD20 mAb other than Obinutuzumab, or other confounding investigational therapies used for the primary treatment of lupus or LN

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced, but they should continue protocol-mandated visits and procedures.

#### **4.6.3 Study and Site Discontinuation**

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include but are not limited to the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.
- Action is deemed necessary based on recommendations from the independent Data Monitoring Committee (iDMC).

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include but are not limited to the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

### **5. ASSESSMENT OF SAFETY**

#### **5.1 SAFETY PLAN**

Obinutuzumab is currently approved in CLL and also has been used in clinical studies for other malignancies such as NHL but not for autoimmune diseases. Thus, the entire safety profile is not known at this time. The safety plan for this study is designed to ensure patient safety and will include specific eligibility criteria and monitoring assessments as detailed below.

##### **5.1.1 Infusion-Related Reactions**

The most frequently observed adverse drug reactions in patients who received obinutuzumab during clinical studies in CLL and NHL were IRRs, which occurred

predominantly during infusion of the first 1000 mg. In patients who received the combined measures for prevention of IRRs (adequate glucocorticoid, oral analgesic/antihistamine, omission of antihypertensive medication in the morning of the first infusion, and, for CLL patients only, the Cycle 1 Day 1 dose administered over 2 days), a decreased incidence of all grade IRRs was observed. The rates of Grades 3–4 IRRs (which were based on a relatively small number of patients) were similar before and after mitigation measures were implemented. The incidence and severity of infusion-related symptoms decreased substantially after the first 1000 mg was infused, with most patients having no IRRs during subsequent administrations of obinutuzumab.

In the majority of patients, IRRs were mild to moderate and could be managed by the slowing or temporary halting of the first infusion, but severe and life-threatening IRRs requiring symptomatic treatment have also been reported. IRRs may be clinically indistinguishable from IgE-mediated allergic reactions (e.g., anaphylaxis).

In studies where patients received either obinutuzumab or rituximab (another anti-CD-20), obinutuzumab patients appeared to have more IRRs compared to those receiving rituximab.

Details regarding management of IRRs can be found in Section [5.1.9](#).

### **5.1.2 Infections**

Serious bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of obinutuzumab therapy. Fatal infections have been reported.

Obinutuzumab is more potent in B-cell depletion than is rituximab; it is theoretically possible that there is an increased risk of infections with obinutuzumab compared with rituximab. Study BO21004/CLL11 provides the most meaningful assessment of the possible risk of infection (Goede et al. 2014). In Stage 1a (obinutuzumab+chlorambucil versus chlorambucil alone) and Stage 2 (obinutuzumab+chlorambucil versus rituximab+chlorambucil) of Study BO21004 in patients with CLL, the incidence of infections was similar between the treatment arms. However, the chlorambucil arm compared with the obinutuzumab+chlorambucil arm showed a higher incidence of serious infections and deaths due to infection; the incidence of serious infections and fatal infections was similar in the obinutuzumab+chlorambucil and rituximab+chlorambucil arms. To date, there is no clear evidence of a difference between rituximab and obinutuzumab regarding infections.

#### **5.1.2.1 Hepatitis B Reactivation**

HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with anti-CD20 antibodies, including obinutuzumab.

### **5.1.2.2      Progressive Multifocal Leukoencephalopathy**

Progressive multifocal leukoencephalopathy (PML) has been reported in patients treated with obinutuzumab. The diagnosis of PML should be considered in any patient that presents with new-onset or changes to preexisting neurologic manifestations. The symptoms of PML are unspecific and can vary depending on the affected region of the brain. Motor symptoms with corticospinal tract findings (e.g., muscular weakness, paralysis, and sensory disturbances), sensory abnormalities, cerebellar symptoms, and visual field defects are common. Some signs/symptoms regarded as “cortical” (e.g., aphasia or visual-spatial disorientation) may occur. Evaluation of PML includes but is not limited to consultation with a neurologist, brain MRI, and lumbar puncture (cerebrospinal fluid testing for John Cunningham [JC] viral DNA). Therapy with obinutuzumab should be withheld during the investigation of potential PML and permanently discontinued in case of confirmed PML. Discontinuation or reduction of any concomitant immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the evaluation and treatment of PML.

### **5.1.3      Immunizations**

The safety of immunization with live or attenuated viral vaccines, following obinutuzumab therapy has not been studied, and vaccination with live virus vaccines is not recommended during treatment and until B-cell recovery.

### **5.1.4      Neutropenia**

Severe and life threatening neutropenia, including febrile neutropenia, has been reported during treatment with obinutuzumab for hematologic malignancies.

### **5.1.5      Thrombocytopenia**

Severe and life threatening thrombocytopenia, including acute thrombocytopenia (occurring within 24 hours after the infusion), has been observed during treatment with obinutuzumab for hematologic malignancy. Fatal hemorrhagic events have also been reported during Cycle 1 in patients treated with obinutuzumab for hematologic malignancy.

### **5.1.6      B-Cell Depletion and Recovery**

B-cell recovery has taken place whenever peripheral B cells are no longer depleted. B-cell peripheral blood depletion is defined as levels below the lower limit of quantification (LLOQ) of the HSFC assay (1 cell/ $\mu$ L). B-cell repopulation is defined as the return of peripheral blood B cells to a level of 10 cells/ $\mu$ L. B-cell recovery is defined as peripheral blood B cells at the patient’s pretreatment baseline or at the LLN for the population under study (25 cells/ $\mu$ L). In the majority of cases, B-cell recovery has taken longer than 12 months in previous studies of obinutuzumab, with and without chemotherapy, for the treatment of hematologic malignancies.

### **5.1.6.1 Obinutuzumab Monotherapy - NHL and CLL Patients**

In the Phase II part of study BO21003 (relapsed indolent NHL), 87 patients were included in the obinutuzumab arm and 86 in rituximab arm. The median level of CD19 cells was  $0.079 \times 10^9$  cells/L at baseline and decreased rapidly to zero by 2.5 hours post-infusion on Cycle 1, Day 1. At the end of the treatment phase, of those with a known B-cell status, 80 of the rituximab patients (95%) and 82 of the obinutuzumab patients (96%) had B-cell depletion. At 18 months post-treatment, 5 of 8 and 17 of 19 patients (who were tested) in the rituximab and obinutuzumab arms, respectively, remained B-cell depleted.

The data from patients with NHL in Studies BO21003 and BO20999 were pooled and analyzed for B-cell depletion (a total of 205 patients). In this population from the pooled analysis, 195 of 202 patients (97%) had B-cell depletion at the end of treatment. At 12 months, 10 of 56 patients (18%) with known B-cell status had recovered B cells.

The data from patients with CLL in Studies BO21003 and BO20999 were pooled and analyzed for B-cell depletion (a total of 38 patients). In this CLL population from the pooled analysis, 30 of 35 patients with available data (86%) had B-cell depletion at the end of treatment. Twenty-seven of these patients had at least 6 months follow-up information (after the last study drug administration), and after 24 months, 19 of 27 patients (70%) had recovered B cells. Of note, there were no B-cell count data on the remaining 30% of patients as they had either progressed or died or were lost to follow-up before this timepoint.

### **5.1.6.2 Obinutuzumab in Combination with Chemotherapy - CLL Patients**

In the Phase III Study BO21004/CLL11, 40 of 44 patients (91%) in the obinutuzumab + chlorambucil arm with available data had B-cell depletion at the end of treatment. Within 24 months after the end of follow-up, 18 of 40 patients (45%) had recovered B-cells, including 5 patients who also experienced disease progression at the time of recovery.

### **5.1.7 Immunoglobulin Depletion and Recovery**

When obinutuzumab has been used for treatment of hematologic malignancies, immunoglobulin depletion and recovery has varied. In Study BO20999 Phase I, for patients with NHL, the levels of IgA, IgG, and IgM immunoglobulins were either low or normal for the duration of the treatment period. For the patients with CLL, immunoglobulin levels were low during the course of treatment. In Phase II, across indications (aggressive NHL, indolent NHL, and CLL), changes in baseline mean and median levels of IgA, IgG, and IgM were observed during the treatment period, but baseline levels had been achieved by the end of the treatment period.

In Study BO21003, in Phase II, in the obinutuzumab arm, mean and median values for IgA, IgG, and IgM concentrations were all within the standard reference ranges.

In Study BO21000, the serum levels of IgA, IgG, and IgM decreased from baseline to Cycle 4 and follow-up (Day 28), but the median levels remained within the corresponding normal ranges. No differences between treatment population or dose groups were observed in either treatment arm.

### **5.1.8 Gastrointestinal Perforations**

In the pivotal study in NHL, cases of GI perforation have been reported in patients treated with obinutuzumab in association with bendamustine. Patients with NHL may have a tumor involvement of the GI tract (very rare in CLL patients), which may shrink rapidly and lead to an opening in the GI wall.

### **5.1.9 Management of Specific Adverse Events**

Guidelines for management of specific adverse events are outlined in [Table 6](#). Additional guidelines are provided in the subsections below.

**Table 6 Guidelines for Management of Specific Adverse Events**

Event	Action to Be Taken
General IRR	<ul style="list-style-type: none"><li>Patients who have pre-existing cardiac or pulmonary conditions should be monitored carefully throughout the infusion and the post-infusion period.</li><li>Withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each obinutuzumab infusion and for the first hour after administration.</li><li>Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their anti-hypertensive medication.</li><li>Hypersensitivity may be difficult to distinguish from IRRs. If a hypersensitivity reaction is suspected during infusion (e.g., symptoms typically occurring after previous exposure and very rarely with the first infusion), the infusion should be stopped and treatment permanently discontinued.</li><li>Patients with known IgE mediated hypersensitivity to obinutuzumab must not be treated.</li><li>For additional guidance see <a href="#">Table 3</a>.</li></ul>
Infections: General	<ul style="list-style-type: none"><li>No patient will be enrolled with an active infection or history of chronic or recurring infections.</li><li>Patients who develop an active infection during the study will have study drug withheld until the event has resolved.</li><li>Patients who require vaccination should be pre-vaccinated 6 weeks prior to receiving study drug.</li><li>Vaccination with live vaccine during study is contra-indicated (see Section <a href="#">4.4.3</a>).</li></ul>
Infections: Hepatitis B	<ul style="list-style-type: none"><li>Hepatitis B screening is required prior to initiation of study drug.</li><li>Patients with active or chronic hepatitis B (surface Ag+) will be excluded from the study.</li><li>Patients who are HBcAb+ with no detectable DNA will be allowed into the study but will require regular monitoring of HBV DNA. If reactivation is seen, study drug treatment must be withheld.</li><li>Patients will be monitored regularly for transaminitis.</li><li>Patients with transaminitis will be promptly referred to a hepatologist for evaluation and treatment.</li><li>Patients with Hepatitis B reactivation, despite the use of appropriate antivirals, will be discontinued from treatment as outlined in Section <a href="#">4.6.2</a>.</li></ul>

CSF = cerebrospinal fluid; GI = gastrointestinal; HBcAb = hepatitis B core antibody;

HBV = hepatitis B virus; IRR = infusion-related reaction; IVIG = intravenous

immunoglobulin; JC = John Cunningham; MRI = magnetic resonance imaging;

PML = progressive multifocal leukoencephalopathy.

**Table 6 Guidelines for Management of Specific Adverse Events (cont.)**

Event	Action to Be Taken
Infections: suspected PML	<ul style="list-style-type: none"> <li>Stop study drug.</li> <li>Obtain neurological consult.</li> <li>In consultation with a neurologist, we recommend obtaining an MRI and performing a lumbar puncture to assess for CSF JC viral DNA.</li> <li>Notify monitors immediately.</li> <li>Study treatment will be withheld for all participants while patient is unblinded and investigated for suspected PML.</li> </ul>
Neutropenia	<ul style="list-style-type: none"> <li>Patients who experience neutropenia should be closely monitored with regular laboratory tests until resolution.</li> <li>If treatment is necessary, it should be administered in accordance with local guidelines and administration of granulocyte colony stimulating factors should be considered.</li> <li>Any signs of concomitant infection should be treated as appropriate.</li> <li>Grade 3 or 4 neutropenia that does not resolve to Grade <math>\leq 2</math> within 8 weeks is a treatment-discontinuation criterion.</li> <li>Cases of late onset neutropenia (occurring 28 days after the end of treatment) or prolonged neutropenia (lasting more than 28 days after treatment has been completed/stopped) have also been reported in studies of obinutuzumab for hematologic malignancy.</li> </ul>
Thrombocytopenia	<ul style="list-style-type: none"> <li>Patients should be closely monitored for thrombocytopenia.</li> <li>If thrombocytopenia occurs, regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia.</li> <li>Transfusion of blood products (i.e., platelet transfusion) according to institutional practice is at the discretion of the treating physician.</li> <li>Thrombocytopenia that does not resolve to Grade <math>\leq 2</math> within 8 weeks is a treatment-discontinuation criterion.</li> <li>Use of all concomitant therapies, which could possibly worsen thrombocytopenia related events such as platelet inhibitors and anticoagulants, should also be taken into consideration</li> </ul>
Hypogammaglobulinemia	<ul style="list-style-type: none"> <li>Ig levels will be monitored throughout the study period.</li> <li>IVIG should be considered for patients with recurrent/severe infections despite appropriate treatment, with concomitant hypogammaglobulinemia.</li> </ul>
GI perforations	<ul style="list-style-type: none"> <li>Promptly evaluate patients presenting with new onset abdominal symptoms.</li> </ul>

CSF=cerebrospinal fluid; GI=gastrointestinal; HBcAb=hepatitis B core antibody;

HBV=hepatitis B virus; IRR=infusion-related reaction; IVIG=intravenous

immunoglobulin; JC=John Cunningham; MRI=magnetic resonance imaging;

PML=progressive multifocal leukoencephalopathy.

## **5.2 SAFETY PARAMETERS AND DEFINITIONS**

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section [5.4](#).

### **5.2.1 Adverse Events**

According to the ICH guidelines for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section [5.3.5.10](#).
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, Xray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

### **5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)**

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.

- Requires or prolongs inpatient hospitalization (see Section [5.3.5.11](#))

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

### **5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)**

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below
 

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- IRRs (see Section 5.1.1)
- Grade 3 or higher infections (see Section 5.1.2)
- Any hepatitis B reactivation and PML (see Section 5.1.2)
- Drug-related neutropenia (see Section 5.1.4)

- Drug-related thrombocytopenia (see Section 5.1.5)
- GI perforations (see Section 5.1.8)

### **5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS**

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections Sections 5.4 – 5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4 ).

#### **5.3.1 Adverse Event Reporting Period**

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

**After informed consent** has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

**After initiation of study drug**, all adverse events, regardless of relationship to study drug, will be reported until the patient completes his or her last study visit at Week 104 or for a period of 76 weeks after the last dose of study drug (whichever is longer). After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6).

#### **5.3.2 Eliciting Adverse Event Information**

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation time-points. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

#### **5.3.3 Assessment of Severity of Adverse Events**

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. **Table 3** will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

**Table 7 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE**

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living <sup>a</sup>
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living <sup>b,c</sup>
4	Life-threatening consequences or urgent intervention indicated <sup>d</sup>
5	Death related to adverse event <sup>d</sup>

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

- <sup>a</sup> Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- <sup>b</sup> Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
- <sup>c</sup> If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.4.2.
- <sup>d</sup> Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

### **5.3.4 Assessment of Causality of Adverse Events**

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 8):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

**Table 8 Causal Attribution Guidance**

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	<u>An adverse event will be considered related, unless it fulfills the criteria specified below.</u> Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

### **5.3.5 Procedures for Recording Adverse Events**

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

#### **5.3.5.1 Infusion-Related Reactions**

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to obinutuzumab infusion should be captured as a diagnosis (e.g., "infusion-related reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

#### **5.3.5.2 Diagnosis versus Signs and Symptoms**

For adverse events other than IRRs (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and

symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

### **5.3.5.3 Adverse Events That Are Secondary to Other Events**

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

### **5.3.5.4 Persistent or Recurrent Adverse Events**

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. Details regarding any increases (or decreases) in severity will be captured on the Adverse Event Intensity or Grade Changes eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation time points and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

### **5.3.5.5 Abnormal Laboratory Values**

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5× ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section [5.3.5.4](#) for details on recording persistent adverse events).

### **5.3.5.6 Abnormal Vital Sign Values**

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

### **5.3.5.7 Abnormal Liver Function Tests**

The finding of an elevated ALT or AST ( $>3 \times \text{ULN}$ ) in combination with either an elevated total bilirubin ( $>2 \times \text{ULN}$ ) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST  $>3 \times \text{ULN}$  in combination with total bilirubin  $>2 \times \text{ULN}$
- Treatment-emergent ALT or AST  $>3 \times \text{ULN}$  in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

### **5.3.5.8 Deaths**

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of SLE.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. *If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").*

If the death is attributed to progression of lupus/SLE, "systemic lupus erythematosus progression" should be recorded on the Adverse Event eCRF.

### **5.3.5.9 Preexisting Medical Conditions**

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

### **5.3.5.10 Lack of Efficacy or Worsening of Systemic Lupus Erythematosus**

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

### **5.3.5.11 Hospitalization or Prolonged Hospitalization**

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

*An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:*

- Hospitalization for respite care
- Planned hospitalization required by the protocol, including initial kidney biopsy and/or study drug administration
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

The patient has not experienced an adverse event

- Hospitalization for routine or scheduled repeat surveillance kidney biopsy

*An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:*

- Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available

### **5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration**

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section [5.4.2](#)).

No safety data related to overdosing of obinutuzumab are available. In clinical studies with obinutuzumab, doses ranging from 50 mg up to and including 2000 mg per infusion have been administered. The incidence and intensity of adverse reactions reported in these studies did not appear to be dose dependent.

## **5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR**

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical study. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (see Section [5.4.2](#) for further details)
- Adverse events of special interest (see Section [5.4.2](#) for further details)
- Pregnancies (see Section [5.4.3](#) for further details)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

#### **5.4.1           Emergency Medical Contacts**

*To ensure the safety of study participants, access to the Medical Monitors is available 24 hours per day, 7 days per week. Details will be provided separately. An Emergency Medical Call Center will also be available 24 hours per day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.*

#### **5.4.2           Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest**

##### **5.4.2.1       Events That Occur prior to Study Drug Initiation**

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

##### **5.4.2.2       Events That Occur after Study Drug Initiation**

After initiation of study drug, serious adverse events and adverse events of special interest will be reported for a period of 52 weeks after the last dose. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section [5.6](#).

#### **5.4.3           Reporting Requirements for Pregnancies**

##### **5.4.3.1       Pregnancies in Female Patients**

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 18 months after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted either by faxing or by scanning and emailing the form using the fax

number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

#### **5.4.3.2      Pregnancies in Female Partners of Male Patients**

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 12 months after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. To allow the Sponsor to collect additional information, the Sponsor will request that the pregnant partner signs an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator will update a Clinical Trial Pregnancy Reporting Form with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

#### **5.4.3.3      Abortions**

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section [5.4.2](#)).

#### **5.4.3.4      Congenital Anomalies/Birth Defects**

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section [5.4.2](#)).

## **5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS**

### **5.5.1 Investigator Follow-Up**

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or study-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section [5.4.3.1](#).

### **5.5.2 Sponsor Follow-Up**

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

## **5.6 POST-STUDY ADVERSE EVENTS**

Post-study, the investigator is not required to actively monitor patients for adverse events; however, the investigator should notify the Sponsor of any death, other serious adverse event, or adverse event of special interest occurring after the end of the adverse event reporting period, believed to be related to treatment, if he or she becomes aware of them.

The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a patient who participated in this study.

The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

## **5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES**

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously

communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities in accordance with applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Obinutuzumab Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting decisions will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An iDMC will monitor the incidence of anticipated adverse events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

## **6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN**

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.

### **6.1 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 Cochrane-Mantel-Haenzel (CMH) test, assuming the same CRR proportions across the strata.

## **6.2 SUMMARIES OF CONDUCT OF STUDY**

The numbers of patients, who enroll, discontinue, and complete the study, will be tabulated by treatment group and study period (treatment or BCFU). Reasons for premature study discontinuation will be listed and summarized by treatment group and study period. Eligibility criteria exceptions and other major protocol deviations will also be summarized by treatment group.

## **6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY**

Demographic and pretreatment characteristics such as age, sex, serum creatinine, proteinuria, MMF/MPA use, treatment, LN class, SLE and nephritis duration, race/ethnicity, weight, British Isles Lupus Assessment Group (BILAG) score, and background therapies for SLE will be summarized by treatment group.

Continuous data (e.g., age, body weight, and height) will be summarized using descriptive statistics (mean, standard deviation, median, minimum, and maximum). For categorical data (e.g., race/ethnicity and sex), the number and percentage of participants in each category will be presented.

## **6.4 EFFICACY ANALYSES**

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.

### **6.4.1 Primary Efficacy Endpoint**

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. Additional criteria for analyses of patients who are considered non-responders will be specified in the SAP.

The proportions of patients achieving CRR across treatment groups will be compared using a 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.

#### **6.4.2 Secondary Efficacy Endpoints**

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  $\leq 15\%$  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  $\leq 3.0$ , 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  $< 3.0$

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.

The percent change from baseline and mean and median assessments of biomarkers of LN disease activity will be analyzed using appropriate statistical methodology.

The proportions of patients who achieve a CRR at Week 24 will be analyzed using the same methodology as the primary analysis. In addition, the modified definitions, mCRR1, mCRR2, and mCRR3, of CRR will be analyzed in this way to assess the sensitivity of CRR to its definition.

Sensitivity analyses will be performed to assess the potential impact on the primary endpoint, and possibly also key secondary endpoints, of missing data and possibly also changes to background immunosuppressive medication.

The secondary, sensitivity, PRO, and exploratory analyses will be fully specified in the SAP.

#### **6.4.3 Exploratory Efficacy Endpoints**

The exploratory outcome endpoints for this study are:

- Change in B-cell subsets over the course of the study
- Change in serum and urine biomarkers over the course of the study
- 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 and Week 36
- Change in Physician's Global Assessment over 52 weeks
- Change in GTCl over 52 weeks
- Change in Renal biopsy histopathology over time

### **6.5 SAFETY ANALYSES**

The safety analyses will include all randomized patients who received any study drug, with patients grouped according to the treatment actually received.

#### **6.5.1 Adverse Events**

Adverse events will be coded according to a standardized thesaurus. The severity of adverse events will be classified using the NCI CTCAE, Version 4.0.

The number and percentage of patients who experience an adverse event will be summarized by mapped term, appropriate thesaurus level, and toxicity grade for each treatment group. Separate summaries will be provided for serious adverse events, treatment-related adverse events (defined as any adverse event occurring during or within 24 hours following the completion of a study drug infusion), infusion-related adverse events and adverse events leading to study discontinuation.

#### **6.5.2 Deaths**

Patient deaths, including the primary cause of death, will be summarized.

#### **6.5.3 Laboratory Tests**

Descriptive statistics of laboratory values and the change from baseline (Day 1) will be presented for each treatment group. The number and percentage of patients with treatment-emergent laboratory abnormalities will be presented for each treatment group. Laboratory measurements will include serum chemistries; urinalysis; hematology; plasma immunoglobulins; and circulating B-cells, T-cells, neutrophils, and other cell populations.

The number and percentage of patients with positive serum antibodies to obinutuzumab at baseline and during the treatment period will be tabulated.

#### **6.5.4 Vital Signs**

The change from pretreatment (measured just before initiation of the infusion) in vital signs recorded during infusion and post-infusion will be summarized. Vital signs that are obtained during screening and the follow-up period will also be summarized.

### **6.6 PHARMACODYNAMIC ANALYSES**

The primary PD marker will be CD19+ B-cell counts. Exploratory PD markers from blood samples will be summarized graphically and descriptively over time by cohort; these markers include B-cell subsets, 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.

Potential PD markers specific to SLE/LN will be summarized graphically and descriptively as appropriate and may include but are not limited to the following:

- Markers of inflammation or B-cell activation: BAFF, proteinuria, and C3 and C4 complement
- Autoantibodies: ANA, anti-dsDNA, Sm, Ro, La, RNP, and others

Exploratory analyses will be performed to assess the possible relationship between obinutuzumab dosing, PD markers, PK measures, and clinical response. The key exploratory analyses will be specified in the SAP.

### **6.7 PHARMACOKINETIC ANALYSES**

PK parameters derived from serum concentrations of obinutuzumab will be computed by the following:

- Maximum serum concentration
  - During the entire study ( $C_{max}$ )
  - After the first course of study drug ( $C_{max1}$ )
  - After the second course of study drug ( $C_{max2}$ )
- AUC from
  - Time 0 to infinity ( $AUC_{0-\infty}$ ) based on all four infusions
  - Time 0 to 336 days ( $AUC_{0-336}$ ) based on all four infusions
  - Time 0 to 168 days ( $AUC_{0-168}$ ) based on the first two infusions
  - Time 168 to 336 days ( $AUC_{168-336}$ ) based on the third and fourth infusions
- Systemic clearance
- Volume of distribution under steady-state conditions ( $V_{ss}$ )

- Half-life ( $t_{1/2}$ ) for the terminal portion of the serum concentration–time curve after both courses of treatment

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 (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.

No hypothesis testing will be performed using the PK parameters. PK data will be summarized using descriptive statistics, including mean, standard deviation, geometric mean, coefficient of variation, median, and range.

Additional PK analyses will be conducted as appropriate.

## **6.8 PATIENT- AND PHYSICIAN-REPORTED OUTCOME ANALYSES**

The Subject's Global Assessment of disease activity VAS and the Physician's Global Assessment of disease activity VAS are recorded at baseline and at Weeks 4, 12, 24, 36, and 52/Early Termination. This assessment will be presented separately from adverse event data. Details will be provided in the SAP.

## **6.9 EXPLORATORY ANALYSES**

The exploratory analyses include the following:

- Change from baseline in proteinuria at Week 52
- Change from baseline in albumin level
- Proportion of subjects that experience a doubling of serum creatinine at Week 52
- Change from baseline in estimated GFR at Week 52
- Change from baseline in the SLICC/ACR damage index at Week 52
- Change from baseline in SLE-associated autoantibodies at Week 52
- Assessment of local versus centralized expert panel assessment of renal biopsies
- Histopathologic assessment of renal biopsies for the presence of CD19+ B cells and other immune cells
  - Change in SLEDAI-2K from baseline to Week 52.

Additional exploratory analyses will be pre-specified in the SAP.

## **6.10 INTERIM ANALYSES**

### **6.10.1 Planned Interim Analyses**

#### **6.10.1.1 Pharmacodynamic Futility Interim Analysis:**

Given the rationale for this study, including the results from the LUNAR (Rovin et al. 2012) and BELONG studies (Mysler et al. 2013), 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 LLOQ of the assay occurred in 46% of patients (Vital et al. 2011). 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  $\geq 11$  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  $\alpha$ -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.

#### **6.10.1.2 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  $\alpha$ -level is not required.

## **7. DATA COLLECTION AND MANAGEMENT**

### **7.1 DATA QUALITY ASSURANCE**

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and other electronic data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

### **7.2 ELECTRONIC CASE REPORT FORMS**

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records.

Acknowledgement of receipt of the compact disc is required.

### **7.3 SOURCE DATA DOCUMENTATION**

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records,

clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical study.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for study-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

#### **7.4 USE OF COMPUTERIZED SYSTEMS**

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

#### **7.5 RETENTION OF RECORDS**

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

*The Sponsor will retain study data for 25 years after the final Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer.*

## **8. ETHICAL CONSIDERATIONS**

### **8.1 COMPLIANCE WITH LAWS AND REGULATIONS**

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the *applicable* laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug application will comply with U.S. FDA regulations and applicable local, state, and federal laws.

*Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trials Directive (2001/20/EC) or Clinical Trials Regulation (536/2014) and applicable local, regional, and national laws.*

### **8.2 INFORMED CONSENT**

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Home Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

### **8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE**

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

## **8.4 CONFIDENTIALITY**

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. Food and Drug Administration and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

*Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.*

## **8.5 FINANCIAL DISCLOSURE**

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., last patient last visit).

## **9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION**

### **9.1 STUDY DOCUMENTATION**

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

## **9.2 PROTOCOL DEVIATIONS**

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. *The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.*

## **9.3 SITE INSPECTIONS**

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

## **9.4 ADMINISTRATIVE STRUCTURE**

During the conduct of this protocol, an IxRS will be implemented to enable appropriate randomization and stratification, and a central laboratory will be employed through a central laboratory vendor. The protocol oversight will include an iDMC, which will meet on a regular predefined basis. Additionally, a centralized renal histopathology reading process will be employed to collect renal biopsy data and enable exploratory analyses of the pathology findings.

## **9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS**

Regardless of the outcome of a study, the Sponsor is dedicated to openly providing information on the study to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. *Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Informations at the following website:*

*<https://www.roche.com/innovation/process/clinical-trials/data-sharing/>*

The results of this study may be published or presented at scientific congresses. For all clinical studies in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical study results within 6 months after the availability of the respective clinical study report. In addition, for all clinical studies in

patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

## **9.6           PROTOCOL AMENDMENTS**

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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## Appendix 1

### Schedule of Assessments

	Week	–4 to 0	Treatment Period							
			1	2	4	12	24	26	36	52/ET
Day	–28 to –1	1 <sup>a</sup>	15	28	84	168	182	252	364	
Informed consent		x								
Inclusion/exclusion criteria		x	x							
Medical history		x	x							
IxRS assignment <sup>b</sup>		x	x							
Demographic data		x								
Subject's Global Assessment <sup>c</sup>			x		x	x		x	x	
Physical exam (limited)		x	x				x			x
Height		x								
Vital signs and weight <sup>d</sup>		x	x	x	x	x	x	x	x	
12-Lead ECG		x								x
Chest X-ray <sup>e</sup>		x								
Physician's Global Assessment			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 <sup>f</sup>		x	x	x	x	x	x	x	x	
Serum chemistries <sup>g</sup>		x	x	x	x	x	x	x	x	
Urinalysis <sup>h</sup>		x	x		x	x	x		x	x

## Appendix 1

### Schedule of Assessments (cont.)

Week	Day	Treatment Period								
		−4 to 0	1 <sup>a</sup>	2	4	12	24	26	36	52/ET
24-hour urine collection <sup>i</sup>		x	x			x	x		x	x
Pregnancy test <sup>j</sup>		x	x	x	x	x	x	x	x	x
HBsAg <sup>k</sup> , HBcAb, Hepatitis C antibody		x								
Autoantibody profile <sup>l</sup>		x	x		x	x	x		x	x
Antibody titers <sup>m</sup>		x					x			x
Serum PK sampling <sup>n</sup>			x <sup>n</sup>	x <sup>n</sup>	x	x	x <sup>n</sup>	x <sup>n</sup>	x	x
Blood sample for flow cytometry <sup>o</sup>			x	x	x	x	x <sup>o</sup>			x
Serum ADAs			x <sup>o</sup>				x <sup>o</sup>			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 <sup>o</sup>		x	x <sup>o</sup>	x	x	x	x <sup>o</sup>		x	x
Plasma for biomarkers <sup>o</sup>		x	x <sup>o</sup>	x	x	x	x <sup>o</sup>		x	x
Urine for biomarkers <sup>p, o</sup>		x	x	x	x	x	x		x	x
PAXgene RNA <sup>o</sup>		x	x <sup>o</sup>	x	x	x	x <sup>o</sup>		x	x
Blood DNA <sup>q</sup> (optional)		x								
Record of menses		x	x	x	x	x	x	x	x	x
Adverse events <sup>r</sup>			x <sup>r</sup>	x <sup>r</sup>	x	x	x <sup>r</sup>	x <sup>r</sup>	x	x

## Appendix 1

### Schedule of Assessments (cont.)

Week	Day	Treatment Period								
		-4 to 0	1	2	4	12	24	26	36	52/ET
	-28 to -1	1 <sup>a</sup>	15	28	84	168	182	252	364	
Concomitant medications		X	X	X	X	X	X	X	X	
Study drug infusion			X <sup>s</sup>	X <sup>s</sup>			X <sup>s</sup>	X <sup>s</sup>		
Corticosteroid dose/taper <sup>t</sup>			X	X	X	X				
Renal biopsy (optional) <sup>u</sup>									(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  $\pm$  3 days of the scheduled visit. Non-infusion visits should be performed within  $\pm$  3 days of the scheduled visit.

- <sup>a</sup> Day 1, unless otherwise notified.
- <sup>b</sup> 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.
- <sup>c</sup> Subject's Global Assessment will be performed prior to other assessments.
- <sup>d</sup> 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).
- <sup>e</sup> 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.
- <sup>f</sup> Hematology: CBC, RBC count, WBC count and differential, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and quantitative platelet count.
- <sup>g</sup> 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 1

### Schedule of Assessments (cont.)

- <sup>h</sup> All urinalyses must include microscopic examination, macroscopic urinalysis, and spot urine protein to creatinine ratio (preferably done on the first morning urine). The spot urine protein to creatinine ratio on Days 1, 84, 168, 252, and 364 must be done from first-morning urine.
- <sup>i</sup> To be analyzed for total protein, total creatinine, creatinine clearance, and protein to creatinine ratio.
- <sup>j</sup> 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.
- <sup>k</sup> 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).
- <sup>l</sup> Autoantibodies include anti-nuclear antibody, anti-dsDNA, Sm, Ro, La, RNP, and anti-C1q.
- <sup>m</sup> Antibody titers include mumps, rubella, *Varicella*, tetanus, influenza, and *S. pneumoniae*.
- <sup>n</sup> 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).
- <sup>o</sup> Samples will be drawn before administration of study drug on dosing days.
- <sup>p</sup> Urine for biomarkers will be processed at the study site. Instructions will be provided in the laboratory manual.
- <sup>q</sup> 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.
- <sup>r</sup> 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.
- <sup>s</sup> 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.
- <sup>t</sup> 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.
- <sup>u</sup> 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 2

### Follow-Up and B-Cell Follow-Up Assessments

Evaluation/Procedure	Follow-Up		B-Cell Follow-Up
Week	76	104	Every 6 Months
Study Day ( $\pm$ 7 days)	532	728	
SLICC/ACR		x	
Serum chemistries <sup>a</sup>	x	x	x
Urinalysis <sup>b</sup>	x	x	x
Urine chemistries: P/C <sup>b</sup>	x	x	x
Pregnancy test <sup>c</sup>	x	x	x
Autoantibody profile <sup>d</sup>	x	x	x
Blood sample for flow cytometry		x	x
Serum ADAs	x	x	x
Serum pharmacokinetics	x	x	x
Quantitative serum Ig levels (total, IgG, IgM, and IgA)	x	x	x
PAXgene RNA	x	x	x
Urine for biomarkers <sup>e</sup>	x	x	x
Serum for biomarkers	x	x	x
Plasma for biomarkers	x	x	x
Adverse events <sup>f</sup>	x	x	x
Glucocorticoid Toxicity Change Index	x	x	
Concomitant medications	x	x	x

ADA=anti-drug antibody; P/C=protein to creatinine ratio; SLICC/ACR=Systemic Lupus International Collaborating Clinics/American College of Rheumatology.

Note: All urine tests should be performed on first-morning urine.

<sup>a</sup> 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.

<sup>b</sup> Microscopic and macroscopic.

<sup>c</sup> For women of childbearing potential, including those who have had a tubal ligation. Urine pregnancy test on Weeks 76 and 104. If result of urine pregnancy test is positive, confirm with a central laboratory serum pregnancy test.

<sup>d</sup> Autoantibodies include: ANA, dsDNA, Sm, Ro, La, RNP, anti-c1q

<sup>e</sup> Urine for biomarkers will be processed at the study site. Instructions will be provided in the laboratory manual.

<sup>f</sup> 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.

**Appendix 3 International Society of Nephrology/Renal Pathology Society (ISN/RPS)  
2003 Classification of Lupus Nephritis**

**Table 1 Classifications**

Class	Description
Class I	Minimal mesangial LN Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence
Class II	Mesangial proliferative LN Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy
Class III	Focal LN Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
Class III (A)	Active lesions: focal proliferative LN
Class III (A/C)	Active and chronic lesions: focal proliferative and sclerosing LN
Class III (C)	Chronic inactive lesions with glomerular scars: focal sclerosing LN
Class IV	Diffuse LN Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) LN when ≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) LN when ≥50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation.
Class IV-S (A)	Active lesions: diffuse segmental proliferative LN
Class IV-G (A)	Active lesions: diffuse global proliferative LN
Class IV-S (A/C)	Active and chronic lesions: diffuse segmental proliferative and sclerosing LN
Class IV-G (A/C)	Active and chronic lesions: diffuse global proliferative and sclerosing LN
Class IV-S (C)	Chronic inactive lesions with scars: diffuse segmental sclerosing LN
Class IV-G (C)	Chronic inactive lesions with scars: diffuse global sclerosing LN

**Appendix 3 International Society of Nephrology/Renal Pathology Society (ISN/RPS)  
2003 Classification of Lupus Nephritis (cont.)**

**Table 1 Classifications (cont.)**

Class	Description
Class V	Membranous LN Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations Class V LN may occur in combination with class III or IV in which case both will be diagnosed. Class V LN may show advanced sclerosis
Class VI	Advanced sclerotic LN ≥90% of glomeruli globally sclerosed without residual activity

A=active; C=chronic; G=global; LN=lupus nephritis; S=segmental.

**Table 2 Definitions**

Term	Definition
Diffuse	A lesion involving most ( $\geq 50\%$ ) glomeruli
Focal	A lesion involving $< 50\%$ of glomeruli
Global	A lesion involving more than half of the glomerular tuft
Segmental	A lesion involving less than half of the glomerular tuft (i.e., at least half of the glomerular tuft is spared)
Mesangial hypercellularity	At least three mesangial cells per mesangial region in a 3 micron thick section
Endocapillary proliferation	Endocapillary hypercellularity due to increased number of mesangial cells, endothelial cells, and infiltrating monocytes, and causing narrowing of the glomerular capillary lumina
Extracapillary proliferation or cellular crescent	Extracapillary cell proliferation of more than two cell layers occupying one fourth or more of the glomerular capsular circumference
Karyorrhexis	Presence of apoptotic, pyknotic, and fragmented nuclei
Necrosis	A lesion characterized by fragmentation of nuclei or disruption of the glomerular basement membrane, often associated with the presence of fibrin-rich material
Hyaline thrombi	Intracapillary eosinophilic material of a homogeneous consistency by which immunofluorescence has been shown to consist of immune deposits
Proportion of involved glomeruli	Intended to indicate the percentage of total glomeruli affected by LN, including the glomeruli that are sclerosed due to LN, but excluding ischemic glomeruli with inadequate perfusion due to vascular pathology separate from LN

LN = lupus nephritis.

Source: Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol* 2004;15:241–50.

**Appendix 3 International Society of Nephrology/Renal Pathology Society (ISN/RPS)  
2003 Classification of Lupus Nephritis (cont.)**

**DEFINITION OF ACTIVE AND CHRONIC LESIONS**

**Active Lesions**

- Endocapillary hypercellularity with or without leukocyte infiltration and with substantial luminal reduction
- Karyorrhexis
- Fibrinoid necrosis
- Rupture of glomerular basement membrane
- Crescents, cellular or fibrocellular subendothelial deposits identifiable by light microscopy (wireloops)
- Intraluminal immune aggregates (hyaline thrombi)

**Chronic Lesions**

- Glomerular sclerosis (segmental, global)
- Fibrous adhesions
- Fibrous crescents

## Appendix 4

### Guidelines for Mycophenolate Mofetil (or Equivalent) Dosing

#### **INITIAL DOSING**

Patients may use either mycophenolate mofetil (MMF) or mycophenolic acid (MPA) as standard of care background therapy in this study. Dosing guidelines are based on use of MMF but an equivalent dose of MPA may be used (MMF 500 mg is equivalent to MPA 360 mg). Patients should be initiated on MMF at a dosage of 1500 mg/day (or equivalent) in divided doses. The target MMF dosage for the protocol is 2000 to 2500 mg/day (or equivalent).

If patients are already receiving MMF (or equivalent) upon entry into the study, their current dosage should be  $\geq$  1500 mg/day (or equivalent); if the dosage is not  $\geq$  1500 mg/day (or equivalent), then it should be increased to that level. The patient's dose should also be divided into two or three times-a-day dosing.

#### **ESCALATION OF DOSE**

The dosage of MMF (or equivalent) should be increased, as tolerated, by 500 mg/week (or equivalent) with the goal of reaching 2000–2500 mg/day (or equivalent), given in divided doses, by Week 4 at the latest.

#### **ADJUSTMENTS TO MMF (OR EQUIVALENT) DOSE**

Investigators will be allowed to adjust the dosage because of tolerance and adverse effects, but the dosage should not be increased to greater than 2500 mg/day (or equivalent). The most common adverse effects requiring titration of MMF (or equivalent) are gastrointestinal (GI) intolerance, neutropenia, and infectious complications (CellCept® U.S. Package Insert [USPI], Myfortic® USPI). To maintain consistency in dose adjustments, recommended reductions are listed in [Table 1](#).

If a patient develops GI toxicity due to MMF (or equivalent), it is recommended to reduce the dose according to “step 1,” as listed in [Table 1](#) if other methods/evaluations, as outlined below, are not helpful. If symptoms persist for 2 weeks after the change, the investigator may reduce the dose according to “step 2,” as listed in [Table 1](#). After the symptoms resolve, an attempt should be made to increase MMF (or equivalent) to a goal of 2000 mg/day (or equivalent) per the previous dosing algorithm. If GI symptoms return, then the patient should be continued on the highest tolerable dose.

GI toxicity may not necessarily require dose reduction of MMF (or equivalent). If diarrhea occurs, infectious causes (e.g., *C. difficile* and enteropathogens) should be ruled out and treated if necessary. If, in the investigator's opinion, the diarrhea is non-infectious, agents such as Lomotil® or tincture of opium may be used to decrease diarrhea.

## **Appendix 4** **Guidelines for Mycophenolate Mofetil (or Equivalent) Dosing** **(cont.)**

If a patient develops an absolute neutrophil count (ANC) between 1000 and 1200, the dose should be reduced according to “step 1,” as listed in [Table 1](#) and the neutrophil count should be checked again at the next scheduled visit. If the ANC continues to be between 1000 and 1200, the dose should be reduced according to “step 2,” as listed in [Table 1](#). After the ANC increases to  $> 1200$ , the dose should be titrated towards goal, but at a rate of 500 mg per month.

If the patient’s ANC is  $< 1000$ , MMF (or equivalent) must be stopped immediately. The patient must return within 14–21 days for repeat measurement of ANC. If ANC is  $> 1500$ , then MMF (or equivalent) may be restarted at the “step 1” dose according to what the patient’s previous MMF (or equivalent) dose was. For example, if the patient’s dosage of MMF was 2500 mg/day at the time of interruption of MMF, then MMF should be restarted at 2000 mg/day.

If a patient experiences an infectious complication, MMF (or equivalent) should be stopped until the episode has resolved. MMF (or equivalent) can then be reinstated at the previous dose.

Regardless of dose reduction, every attempt must be made to bring the patient’s dosage of MMF (or equivalent) to  $\geq 1500$  mg/day (or equivalent).

**Table 1 Protocol-Specified MMF (or Equivalent) Dose Reduction**

MMF dosage (mg/day)	Step 1 Reduction (mg)	Step 2 Reduction (mg)
2500	2000	1500
2250	1750	1250
2000	1500	1000
1500	1000	750

### **REFERENCE**

Hogg RJ, Wyatt RJ, Scientific Planning Committee of the North American IgA Nephropathy Study. A randomized controlled trial of mycophenolate mofetil in patients with IgA nephropathy. *BMC Nephrol* 2004;5:3.

## Appendix 5

### Initial Prednisone/Prednisolone Tapering Schedule

Patients will receive both intravenous (IV) and oral corticosteroids as part of their initial course of therapy. IV methylprednisolone will be dosed at 1000 mg to treat active lupus nephritis (LN) according to standard clinical practice, which typically recommends one to three infusions of methylprednisolone at this dose. Between one and three infusions of 1000 mg methylprednisolone will be allowed for the inclusion of patients into this protocol and can occur at any time before or during the screening interval. For instance, a patient with LN may have been identified in the community prior to referral to the investigator's site and received 1000 mg of methylprednisolone. This dose and all doses of steroids must be accounted for in the steroid concomitant medications section of the case report form. The target protocol methylprednisolone dose is a single 1000 mg infusion, but up to three infusions will be acceptable for study entry.

The initial oral prednisone dose will be 0.50 mg/kg/day, not to exceed 60 mg, and will be given on Days 2–16, excluding concomitant dosing of IV methylprednisolone.

Investigators are instructed to round the calculated dose to the nearest 10-mg increment listed in [Table 1](#). The investigator should instruct the patient to initiate a corticosteroid taper beginning on Day 16. The patient's initial study prednisone dose (or equivalent) is listed on the top line of [Table 1](#), and the subsequent doses, changing every 2 weeks, are noted in the column below the selected initial dose. Patients whose calculated prednisone dose would be >60mg/day should use 60 mg/day as their starting dose.

**Table 1 Prednisone Tapering Schedule**

Starting Prednisone Dose (mg/day)	30	40	50	60
Day 16	25	35	40	50
Day 28	25	30	30	40
Day 42	20	25	20	30
Day 56	15	20	15	20
Day 70	10	15	10	10
Day 84	7.5	7.5	7.5	7.5

#### **CORTICOSTEROID DOSING FOR EXTRARENAL FLARES**

To maintain consistency in the use of corticosteroids for extrarenal flares, patients will not be allowed to increase their prednisone dose during their participation in the study unless it is judged clinically appropriate by the investigator. A flare is defined as an increase in Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)-2K that is not accounted for by either hypocomplementemia or an increase in anti-dsDNA antibody level or the initiation of new immunosuppressive therapy or an increase of corticosteroid

## Appendix 5

### Initial Prednisone/Prednisolone Tapering Schedule (cont.)

dose. On the basis of the severity of the disease, patients may be retreated with prednisone up to 1.0 mg/kg. IV corticosteroids in equivalent doses may be allowed if gastrointestinal involvement temporarily precludes oral corticosteroid use.

Because it is important to maintain a consistent corticosteroid taper to interpret the results of this clinical study, it is suggested that investigators round the calculated corticosteroid dose (based on the patient's weight in kilograms) to the nearest 10-mg increment listed in [Table 2](#) (not to exceed 60 mg/day) and follow the recommended tapering schedule. The investigator should instruct the patient to initiate a corticosteroid taper 14 days after starting the increased corticosteroid dose. The patient's increased study prednisone dosage (or equivalent) is listed on the top line of [Table 2](#), and the subsequent dosages, changing every 2 weeks, are noted in the column below the selected initial dose. If the investigator determines that a higher dose or longer treatment period is necessary, he or she should first contact the Medical Monitor to discuss this. Patients who do not show improvement in their symptoms after 2 weeks of increased corticosteroid treatment are considered to be nonresponsive to corticosteroids.

Patients who initiate a new immunosuppressive or any other new systemic lupus erythematosus medication will return for all protocol-scheduled visits and will not receive further study drug.

**Table 2 Prednisone Dosing Recommendations for Extrarenal Flares**

Starting Prednisone Dose (mg/day)	20	30	40	50	60
Day 16	15	25	30	40	50
Day 30	10	20	25	30	40
Day 44	10	10	15	20	30
Day 58	7.5	10	10	10	20
Day 72	7.5	7.5	10	10	10
Day 86	7.5	7.5	7.5	7.5	7.5

### **CORTICOSTEROID DOSING FOR RENAL FLARES**

To maintain consistency in the treatment of renal flares, retreatment with higher doses of corticosteroids is permitted if judged clinically appropriate by the investigator and if patients meet the criteria for a renal flare as defined by all of the following:

- Stable or increased creatinine

## Appendix 5

### Initial Prednisone/Prednisolone Tapering Schedule (cont.)

- Worsening active urinary sediment from baseline, as defined by a  $\geq 50\%$  increase in RBCs/high-power field or the appearance of new RBC casts when none were previously present
- Increase in proteinuria, as evidenced by an increase in the urine protein to creatinine ratio to  $> 2$ , if the most recent urine protein to creatinine ratio was  $< 2$ .

Patients may be treated with prednisone (up to 0.5 mg/kg; not to exceed 60 mg/day) for 2 weeks. Prednisone will then be tapered to achieve  $\leq 10$  mg/day 6 weeks after the initial corticosteroid increase (see [Table 3](#)). Patients who do not exhibit a response to the initial 2 week course of increased corticosteroids, as evidenced by an improvement in urinary sediment and/or a reduction in the urine protein to creatinine ratio, or who initiate a new immunosuppressive therapy will be deemed treatment failures and continue scheduled protocol visits of the study and will not receive additional study drug.

**Table 3 Prednisone Dosing Recommendations for Renal Flares**

Days after Initial Corticosteroid Increase	Prednisone Dose (mg/day)				
	20	30	40	50	60
14	15	25	30	40	50
21	15	20	25	30	40
28	10	20	20	20	30
35	10	15	15	15	20
42	10	10	10	10	10

## **Appendix 6** **Criteria for Classification of Systemic Lupus Erythematosus**

There are 11 criteria for the classification of systemic lupus erythematosus (SLE). On the basis of this classification, a patient would be considered to have “definite” SLE if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.

In this study, a patient will be considered to have SLE if he or she has at least four criteria present, one of which must be a positive anti-nuclear antibody (Criterion 11).

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

**Appendix 6**  
**Criteria for Classification of Systemic Lupus Erythematosus**  
**(cont.)**

Criterion	Definition
9. Hematologic disorder	a) Hemolytic anemia--with reticulocytosis OR b) Leukopenia: $<4,000/\text{mm}^3$ total on 2 or more occasions OR c) Lymphopenia: $<1,500/\text{mm}^3$ on 2 or more occasions OR d) Thrombocytopenia: $<100,000/\text{mm}^3$ in the absence of offending drugs
10. Immunologic disorder <sup>a</sup>	a) Anti-DNA: antibody to native DNA in abnormal titer OR b) Anti-SM: presence of antibody to SM nuclear antigen OR c) Positive finding of antiphospholipid antibodies based on (1) an abnormal serum level of IgG or IgM anti-cardiolipin antibodies, (2) a positive test result for lupus anticoagulant using a standard method, or (3) a false positive serologic test for syphilis known to be positive for $\geq 6$ months and confirmed by <i>Treponema pallidum</i> immobilization or fluorescent treponemal antibody absorption test
11. Anti-nuclear antibody	An abnormal titer of anti-nuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

<sup>a</sup> The modifications to criterion number 10 were made in 1997 (Hochberg 1997).

Source: Tan et al. 1982.

**REFERENCE**

Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40(9):1725.

Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25(11):1271–7.

## Appendix 7

### Study Drug Administration

#### **ADMINISTRATION OF STUDY DRUG**

Study drug (obinutuzumab or placebo) should be given as a slow intravenous (IV) infusion. It should not be administered as an IV push or bolus.

Although obinutuzumab may be administered on an outpatient basis, patients may be hospitalized for observation at the discretion of the investigator. Irrespective, obinutuzumab must be administered in a hospital or clinic environment where full resuscitation facilities are immediately available and under close supervision of the investigator or designee. The guidelines below may be slowed at the discretion of the investigator based on a patient's clinical presentation.

#### **FIRST INFUSION (DAY 1)**

Patients should receive prophylactic treatment of acetaminophen (650–1000 mg) and diphenhydramine hydrochloride (HCl) (50 mg; or equivalent dose of a similar agent) by mouth 30–60 minutes prior to the start of an infusion. Prior to the Day 1 infusion, patients must receive 80 mg IV methylprednisolone or placebo 30–60 minutes prior to the start of the study drug infusion.

NOTE: Patients should be cautioned not to operate vehicles or hazardous machinery until their response to diphenhydramine (or similar antihistamine) has been determined.

Study drug infusions should be made through a dedicated line and commence at a rate of 50 mg/hr. This may be escalated at a rate of 50 mg/hr every 30 minutes to a maximum of 400 mg/hr. [Table 1](#) presents the schedule for the first infusion.

**Table 1 Schedule for First Infusion**

Time (min)	Infusion Rate		Dose in 30 minutes (mg)	Cumulative Dose (mg)
	(mg/hr)	(mL/hr)		
0–30	50	12.5	25	25
31–60	100	25	50	75
61–90	150	37.5	75	150
91–120	200	50	100	250
121–150	250	62.5	125	375
151–180	300	75	150	525
181–210	350	87.5	175	700
212–240	400	100	200	900
241–255 <sup>a</sup>	400	100	200	1000

<sup>a</sup> Should complete at 255 minutes (4 hours, 15 minutes) to complete total dose of 1000 mg.

## **Appendix 7** **Study Drug Administration (cont.)**

If a patient experiences a mild infusion-related reaction (IRR) that is deemed by the investigator to be clinically significant, the infusion rate should be reduced to half the infusion rate that was used at the time of the reaction (e.g., from 100 mg/hr to 50 mg/hr). After the reaction has resolved, the infusion should be kept at the reduced rate for an additional 30 minutes. If the reduced rate is tolerated, then the infusion rate may be increased to the next closest rate on the infusion schedule. Patients who experience a moderate-to-severe IRR should have their infusion interrupted immediately and should receive aggressive symptomatic treatment. The infusion should not be restarted before all the symptoms have disappeared; after all symptoms have disappeared, the infusion may be restarted at half the rate. If the reduced rate is tolerated for 30 minutes, then the infusion rate may be increased to the next closest rate on the infusion table.

After the end of the first infusion, the IV line should remain in situ for at least 2 hours to be able to administer drugs intravenously if necessary. At the end of the remaining infusions, the IV line should remain in place for at least 30 minutes. If no adverse events occur during this period of time, the IV line may be removed.

### **SUBSEQUENT INFUSIONS (DAYS 15, 168, AND 182)**

Patients should receive prophylactic treatment of acetaminophen (650–1000 mg) and diphenhydramine HCl (50 mg; or equivalent dose of similar agent) by mouth 30–60 minutes prior to the start of an infusion. Patients must receive 80 mg IV methylprednisolone or placebo 30–60 minutes prior to the start of the study drug infusion.

Patients who tolerated the first infusion of study drug well may receive the second infusion as detailed in [Table 2](#). Patients who experienced an IRR to the first infusion, deemed by the investigator to be clinically significant, should receive study drug as per the initial infusion schedule, with the starting rate of infusion not exceeding half that associated with the prior reactions. If the infusion reaction during the first infusion occurred at a rate >200 mg/hr, then the second infusion rate should start at 100 mg/hr.

Study drug infusions should be made through a dedicated line and commence at a rate of 100 mg/hr. This may be escalated at a rate of 100 mg/hr every 30 minutes to a maximum of 400 mg/hr. [Table 2](#) presents the schedule for the second and subsequent infusions.

In the event that the patient experiences an IRR, the infusion rate should be reduced to half that rate (e.g., from 100 mg/hr to 50 mg/hr). Patients who experience a moderate-to-severe IRR should have their infusion interrupted immediately and should receive aggressive symptomatic treatment. The infusion should not be restarted before all the symptoms have disappeared (see above).

## Appendix 7

### Study Drug Administration (cont.)

Note: These recommendations do not address life-threatening events, including anaphylaxis, for which all appropriate standard measures (including full resuscitation medications and equipment) must be available and should be used as clinically indicated.

**Table 2 Schedule for Second and Subsequent Infusions**

Time (min)	Infusion Rate		Dose in 30 minutes (mg)	Cumulative Dose (mg)
	(mg/hr)	(mL/hr)		
0–30	100	25	50	50
31–60	200	50	100	150
61–90	300	75	150	300
91–120	400	100	200	500
121–150	400	100	200	700
151–180	400	100	200	900
181–195 <sup>a</sup>	400	100	200	1000

<sup>a</sup> Should complete at 195 minutes (3 hours, 15 minutes) to complete total dose of 1000 mg.

## Appendix 8 Corticosteroid Equivalence Chart

	Equivalent Dose (mg)
Hydrocortisone	20
Cortisone acetate	25
Prednisone	5
Prednisolone	5
Methylprednisolone	4
Dexamethasone	0.75
Betamethasone	0.75
Triamcinolone	4
Beclometasone	0.75

Note: Cortisol (hydrocortisone) is the standard of comparison for glucocorticoid potency.

Hydrocortisone is the name used for pharmaceutical preparations of cortisol.

## **Appendix 9** **Instructions for Collecting and Analyzing Urine Samples**

### **BASED ON THE EUROPEAN URINALYSIS GUIDELINES [2000]**

#### **URINE COLLECTION**

Urine collected at Screening; Day 1; and Weeks 12, 24, 36, and 52 should be collected in the following manner:

- A 24-hour urine sample must be initiated prior to the visit, at which point it is to be collected and include only one first-morning urine.
- A separate first-morning urine on the day of the visit should be collected.
- The investigator will take a 30-mL aliquot of urine from the first-morning urine sample for urine sediment analysis (as outlined below), macroscopic analysis, and a spot urine protein to creatinine ratio. The recommended volume of urine collected should be 30 mL, but a minimum of 18 mL should be collected. Please refer to the Central Laboratory Manual for details.

It is preferable that all of the urine for the 24-hour urine collection is collected separately from the first morning sample used for urine sediment analysis, macroscopic analysis, and a spot urine protein to creatinine ratio. If the first morning urine on the day of the visit is the final urine collected for the 24-hour urine collection, then aliquots, as described above, should be taken for urine sediment analysis, macroscopic analysis, and a spot urine protein to creatinine ratio; the leftover urine should be combined with the rest of the 24-hour urine collection, and an aliquot should be taken and sent for creatinine, protein, and protein to creatinine measurement.

For all other visits requiring a urine specimen, every effort should be made to collect a first-morning urine sample. If a first-morning urine sample cannot be collected, then a second-morning urine sample should be collected. If a second-morning urine sample cannot be collected, the patient should be asked to come back within the window period for that visit to give a first- or second-morning urine sample (first-morning urine is preferable). Aliquots as described above should be taken for these samples as well (i.e., one sample for macroscopic analysis, one for urine sediment analysis, and one for a spot protein to creatinine ratio).

Written instructions should be given to the patient about how to collect a morning urine sample. In addition, it is encouraged to remind the patient that strenuous physical exercise should be avoided for the 72 hours preceding a urine collection.

In females, urine collection should be avoided during menstruation.

## **Appendix 9** **Instructions for Collecting and Analyzing Urine Samples (cont.)**

### **URINE EXAMINATION**

Four hours is the maximum recommended time between urine collection and local microscopic analysis.

The recommended volume of urine collected should be 30 mL, but a minimum of 18 mL should be collected.

The sample should be split into three equal aliquots. One aliquot will be used for central laboratory macroscopic and microscopic urinalyses, one aliquot will be used for measurement of spot urine protein to creatinine ratio, and the remaining aliquot will be used for local microscopic analysis. Please refer to the Central Laboratory manual for details.

Local urine microscopic analysis should be performed by manual evaluation. If this cannot be done, validated automated analysis is acceptable, but the Principal Investigator should first discuss the use of the method with the Medical Monitor. The procedure below outlines the recommended process for manual evaluation.

Preparation for microscopic analysis is as follows:

- The aliquot for microscopic analysis should be centrifuged between 400 and  $1500 \times g$  for approximately 5 minutes ( $1000 \times g$  for 5 minutes is preferred).
- The supernatant should be decanted.
- After decanting, if supravital staining will be used to aid in particulate analysis, 10% volume of the supravital stain to be used should be added and the solution mixed gently.
- The sediment should be gently resuspended and then placed onto a microscope slide.
- A coverslip should be added horizontally to maximize even distribution.

## **Appendix 9**

### **Instructions for Collecting and Analyzing Urine Samples (cont.)**

#### **VISUAL MICROSCOPIC ANALYSIS**

- Equipment/staining: If available, it is recommended that phase-contrast microscopy be used if supravital stain is not added for particulate analysis.
- Examination

The sample should first be viewed under low-power magnification to note the presence of casts (red cell casts and white cell casts).

The sample should then be viewed under high-power magnification, and the number of different particles per high-power objective field should be counted. The number of specific particles, (specifically RBCs and WBCs) should be reported as an average observed in at least 10 fields selected from all areas of the coverslip and reported as number of specific particle (either RBC or WBC) per high-power field (HPF). Automated quantification of RBCs and WBCs is acceptable.

In terms of casts, the number and type of casts should be reported as an absolute number as seen in the whole sample and not as an average per HPF. If the absolute number of casts cannot be reported, then it is important to note whether casts are present or absent and, if casts are present, the type of casts. If casts are present, reporting a range is allowed (as long as that range does not include "0").

**Appendix 10**  
**Systemic Lupus International Collaborating Clinics/**  
**American College of Rheumatology (SLICC/ACR)**

**(Sample Case Report Form; Not to Be Used to Enter Subject Data)**

**NOTE:** Damage (nonreversible change, not related to active inflammation) occurring since onset of lupus, ascertained by clinical assessment and present for **at least 6 months** unless otherwise stated. **Repeat episodes must occur 6 months apart to score 2.** The same lesion cannot be scored twice.

		<b>Score</b>	
<b>Item</b>		Not Present	Present
Ocular (either eye, by clinical assessment)	Any cataract ever	<input type="checkbox"/> 0	<input type="checkbox"/> 1
	Retinal change or optic atrophy	<input type="checkbox"/> 0	<input type="checkbox"/> 1
Neuropsychiatric	Cognitive impairment (e.g., memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance levels) or major psychosis	<input type="checkbox"/> 0	<input type="checkbox"/> 1
	Seizures requiring therapy for 6 months	<input type="checkbox"/> 0	<input type="checkbox"/> 1
	Cerebrovascular accident (CVA) ever (score 2 > 1 CVA)	<input type="checkbox"/> 0	<input type="checkbox"/> 1 <input type="checkbox"/> 2
	Cranial or peripheral neuropathy (excluding optic)	<input type="checkbox"/> 0	<input type="checkbox"/> 1
	Transverse myelitis	<input type="checkbox"/> 0	<input type="checkbox"/> 1
Renal	Estimated or measured glomerular filtration rate < 50 mL/min	<input type="checkbox"/> 0	<input type="checkbox"/> 1
	Proteinuria $\geq$ 3.5 gm/24 hours	<input type="checkbox"/> 0	<input type="checkbox"/> 1
	<b>OR</b>		
	End-stage renal disease (regardless of dialysis or transplantation)	<input type="checkbox"/> 0	<input type="checkbox"/> 3
Pulmonary	Pulmonary hypertension (right ventricular prominence, or loud P2)	<input type="checkbox"/> 0	<input type="checkbox"/> 1
	Pulmonary fibrosis (physical and radiograph)	<input type="checkbox"/> 0	<input type="checkbox"/> 1
	Shrinking lung (radiograph)	<input type="checkbox"/> 0	<input type="checkbox"/> 1
	Pleural fibrosis (radiograph)	<input type="checkbox"/> 0	<input type="checkbox"/> 1
	Pulmonary infarction (radiograph)	<input type="checkbox"/> 0	<input type="checkbox"/> 1

**Appendix 10**  
**Systemic Lupus International Collaborating Clinics/**  
**American College of Rheumatology (SLICC/ACR) (cont.)**

		<b>Score</b>	
<b>Item</b>		Not Present	Present
Cardiovascular	Angina or coronary artery bypass	<input type="checkbox"/> 0	<input type="checkbox"/> 1
	Myocardial infarction (MI) ever (score 2 if > 1 MI)	<input type="checkbox"/> 0	<input type="checkbox"/> 1 <input type="checkbox"/> 2
	Cardiomyopathy (ventricular dysfunction)	<input type="checkbox"/> 0	<input type="checkbox"/> 1
	Valvular disease (diastolic murmur, systolic murmur > 3/6)	<input type="checkbox"/> 0	<input type="checkbox"/> 1
	Pericarditis for 6 months, or pericardectomy	<input type="checkbox"/> 0	<input type="checkbox"/> 1
Peripheral vascular	Claudication for 6 months	<input type="checkbox"/> 0	<input type="checkbox"/> 1
	Minor tissue loss (pulp space)	<input type="checkbox"/> 0	<input type="checkbox"/> 1
	Significant tissue loss ever (e.g., loss of digit or limb) (score 2 if > 1 site)	<input type="checkbox"/> 0	<input type="checkbox"/> 1 <input type="checkbox"/> 2
	Venous thrombosis with swelling, ulceration, or venous stasis	<input type="checkbox"/> 0	<input type="checkbox"/> 1
Gastrointestinal	Infarction or resection of bowel below duodenum spleen, liver, or gall bladder ever, for cause any (score 2 if > 1 site)	<input type="checkbox"/> 0	<input type="checkbox"/> 1 <input type="checkbox"/> 2
	Mesenteric insufficiency	<input type="checkbox"/> 0	<input type="checkbox"/> 1
	Chronic peritonitis	<input type="checkbox"/> 0	<input type="checkbox"/> 1
	Stricture or upper gastrointestinal tract surgery ever	<input type="checkbox"/> 0	<input type="checkbox"/> 1
Musculoskeletal	Muscle atrophy or weakness	<input type="checkbox"/> 0	<input type="checkbox"/> 1
	Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis)	<input type="checkbox"/> 0	<input type="checkbox"/> 1
	Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	<input type="checkbox"/> 0	<input type="checkbox"/> 1
	Avascular necrosis (score 2 if > 1)	<input type="checkbox"/> 0	<input type="checkbox"/> 1 <input type="checkbox"/> 2
	Osteomyelitis	<input type="checkbox"/> 0	<input type="checkbox"/> 1

**Appendix 10**  
**Systemic Lupus International Collaborating Clinics/**  
**American College of Rheumatology (SLICC/ACR) (cont.)**

		<b>Score</b>	
<b>Item</b>		Not Present	Present
Skin	Scarring chronic alopecia	<input type="checkbox"/> 0	<input type="checkbox"/> 1
	Extensive scarring or panniculitis other than scalp and pulp space	<input type="checkbox"/> 0	<input type="checkbox"/> 1
	Skin ulceration (excluding thrombosis) for > 6 months	<input type="checkbox"/> 0	<input type="checkbox"/> 1
	Premature gonadal failure	<input type="checkbox"/> 0	<input type="checkbox"/> 1
	Diabetes (regardless of treatment)	<input type="checkbox"/> 0	<input type="checkbox"/> 1
	Malignancy (exclude dysplasia) (score 2 if > 1 site)	<input type="checkbox"/> 0	<input type="checkbox"/> 1 <input type="checkbox"/> 2

**REFERENCE**

Gladman D, Ginzler E, Goldsmith C, et al. The development and initial validation of the systemic lupus international collaborating clinics/American College of Rhumatology Damage Index for systemic lupus erythematosus. *Arthritis Rheum* 1996;39:363–9.

## Appendix 11 Subject's Global Assessment

*Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.*

### (Sample Case Report Form; Not to Be Used to Enter Subject Data)

SUBJECT'S GLOBAL ASSESSMENT (SCREENING)			
<input type="checkbox"/> Check if assessment was not done			
Date of Assessment: _____			
Mo	-	Day	-
Yr			
Please answer the following question by placing a <u>vertical mark through the line</u> .			
<b>Global Assessment of Disease Activity</b>			
On the line below, considering all the ways your SLE affects you, where would you rate your SLE symptoms over the last 10 days?			
None	—————	Severe	
Site Measurement: _____ mm			
<b>Use the original document provided by sponsor</b> <b>Do not photocopy the document since this may alter the length of the 100 mm line</b>			

## Appendix 12

### Physician's Global Assessment

***Do not reproduce or distribute.*** The Sponsor will provide sites with all instruments to be completed in this study.

**(Sample Case Report Form; Not to Be Used to Enter Subject Data)**

### **Physician's Global Asessment (Screening)**

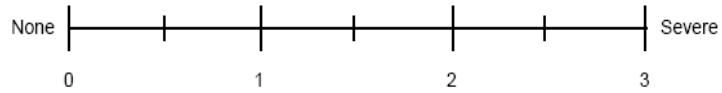
Check if assessment was not done

Date of Assessment: \_\_\_\_\_ - \_\_\_\_\_ - \_\_\_\_\_  
Mo Day Yr

Please answer the following question by placing a vertical mark through the line.

### Global Assessment of Disease Activity

On the line below, where would you rate the subject's SLE over the past 10 days?



mm

Rater Initials:

Use the original document provided by sponsor  
Do not photocopy the document since this may alter the length of the 100 mm line

## Appendix 13

### Systemic Lupus Erythematosus Disease Activity Index-2K

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Circle in SLEDAI Score column if descriptor is present at the time of the visit or in the preceding 10 days

SLEDAI SCORE	Descriptor	Definition
8	Seizure	Recent onset, exclude metabolic, infectious or drug causes
8	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behaviour. Exclude ureaemia and drug causes
8	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes
8	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudates or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes
8	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves
8	Lupus headache	Severe, persistent headache; may be migrainous, but must be non-responsive to narcotic analgesia
8	CVA	New onset Cerebrovascular accident(s). Exclude arteriosclerosis
8	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages or biopsy or angiogram proof of vasculitis
4	Arthritis	≥ 2 joints with pain and signs of inflammation (i.e. tenderness, swelling or effusion)
4	Myositis	Proximal muscle aching/weakness, associated with elevated creatinine phosphokinase (CK)/aldolase, or EMG changes or a biopsy showing myositis
4	Urinary casts	Heme-granular or RBC casts
4	Hematuria	> 5 RBC/high power field. Exclude stone, infection or other cause
4	Proteinuria	> 0.5 gram/24 hours
4	Pyuria	> 5 WBC/high power field. Exclude infection
2	Rash	Inflammatory type rash
2	Alopecia	Abnormal, patchy or diffuse loss of hair
2	Mucosal ulcers	Oral or nasal ulcerations
2	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening
2	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion or ECG or echocardiogram confirmation
2	Low complement	Decrease in CH50, C3 or C4 below lower limit of normal for testing laboratory
2	Increased DNA binding	Increased DNA binding above normal range for testing laboratory
1	Fever	> 38°C. Exclude infectious cause
1	Thrombocytopenia	< 100 × 10 <sup>9</sup> platelets/L, exclude drug causes
1	Leukopenia	< 3 × 10 <sup>9</sup> WBC/L, exclude drug causes

TOTAL SCORE:

## Appendix 14

### Glucocorticoid Toxicity Change Index

#### **COMPOSITE GLUCOCORTICOID TOXICITY CHANGE INDEX**

1. Body mass index (BMI) (compared to baseline)
  - a) Improvement (in either direction) by more than 2 BMI units toward normal BMI (normal range = 18.5–24.9 kg/m<sup>2</sup>)
  - b) No significant change (BMI remains within  $\pm 2$  BMI units compared with baseline) or BMI remains within the normal range
  - c) Moderate increase in BMI (increase by more than 2 but less than 5 BMI units to above the upper limit of normal BMI [24.9 kg/m<sup>2</sup>])
  - d) Major increase in BMI (increase by more than 5 BMI units to above normal BMI [24.9 kg/m<sup>2</sup>])
2. Glucose tolerance (compared to baseline)
  - a) Improvement in glucose tolerance:
    - HbA1c (glycosylated hemoglobin) declined  $> 10\%$  from baseline without medication increase
      - or
    - Decrease in diabetic medication without an increase in HbA1c of  $> 10\%$  or HbA1c  $< 5.7\%$
  - b) No significant change in glucose tolerance:
    - HbA1c within 10% of baseline or HbA1c  $< 5.7\%$  and no change in medication
      - or
    - HbA1c increased to  $> 10\%$  of baseline due to a decrease in medication
      - or
    - Improvement in glucose tolerance  $> 10\%$  due to an increase in medication
  - c) Worsening of glucose tolerance or medication status:
    - HbA1c increased to  $> 10\%$  and HbA1c  $> 5.7\%$  without a change in medication
      - or
    - Increase in diabetic medication with  $< 10\%$  increase in HbA1c
  - d) Worsening of glucose tolerance despite treatment:
    - HbA1c  $> 5.7\%$  and increased to  $> 10\%$  of baseline and an increase in diabetic medication
3. Blood pressure (BP) (compared to baseline)
  - a) Improvement in BP:

## **Appendix 14** **Glucocorticoid Toxicity Change Index (cont.)**

- Decrease in BP of >10% of baseline without medication increase  
or
- Decrease in medication without an increase in BP of >10% or systolic BP  $\leq$  120 and diastolic BP  $\leq$  85

b) No significant change in BP:

- BP within 10% of baseline or systolic BP  $\leq$  120 and diastolic BP  $\leq$  85 and no change in medication  
or
- Deterioration in either systolic or diastolic BP >10% due to a decrease in medication  
or
- An improvement in either systolic or diastolic BP of >10% due to an increase in medication

c) Worsening of hypertension:

- Increase in BP of >10% such that the systolic BP exceeds 120 mmHg or the diastolic BP exceeds 85 mmHg without a change in medication  
or
- Increase in anti-hypertensive medication without an improvement in BP >10%

d) Worsening of hypertension despite treatment:

- Increase in BP of >10% such that the systolic BP exceeds 120 mmHg or the diastolic BP exceeds 85 mmHg and an increase in medication

4. Hyperlipidemia (compared to baseline)

a) Improvement in lipids:

- Decrease in low-density lipoprotein (LDL) concentration >10% of baseline without medication increase toward the target range  
or
- Decrease in medication without an increase in LDL of >10% or LDL remains within target range

b) No significant change in LDL:

- LDL within 10% of baseline or within the target range for patient and no change in medication  
or

## **Appendix 14** **Glucocorticoid Toxicity Change Index (cont.)**

- Increase in LDL >10% due to a decrease in medication
  - or
- Improvement in LDL of >10% due to an increase in medication

c) Worsening of LDL or medication status:

- Increase in LDL of >10% to above target range without increase in medication
  - or
- Increase in medication without >10% change in LDL

d) Worsening of LDL despite treatment:

- Increase in LDL of >10% and an increase in medication

5. Steroid myopathy

- a) No steroid myopathy
- b) Mild steroid myopathy (weakness without functional limitation)
- c) Moderate steroid myopathy (weakness with functional limitation)

See steroid myopathy definitions below.

6. Skin

- a) No skin toxicity
- b) Mild
- c) Moderate

See skin definitions below.

7. Neuropsychiatric

- a) No neuropsychiatric symptoms
- b) Mild
- c) Moderate

See neuropsychiatry definitions below.

8. Infection (since last assessment)

- a) No significant infection
- b) Specific infections <Grade 3 (oral or vaginal candidiasis, uncomplicated zoster)
- c) Grade 3

See infection notes below.

## Appendix 14 Glucocorticoid Toxicity Change Index (cont.)

9. Bone mineral density (BMD) (compared to baseline)
  - a) Improvement – increase in BMD by > 3%
  - b) No significant change (BMD between – 3% and + 3%)
  - c) Deterioation – decrease by ≥ 3%

Percentage (%) refers to total BMD in gms/cm<sup>2</sup>.

If BMD not evaluated, then option “b” should be selected.

### **GLUCOCORTICOID-INDUCED MYOPATHY DEFINITIONS**

- Glucocorticoid-induced myopathy is defined as mild symmetrical weakness of the proximal muscles and/or neck flexors associated with steroid therapy and not due to any other apparent cause. Muscle enzymes are typically within normal limits.
- Mild and moderate myopathy are defined by muscle strength of 4 on the standard Medical Research Council strength testing scale. A 4 means weaker than normal but greater than anti-gravity strength.
- “Mild” is Grade 4 weakness that does not functionally limit the patient.
- “Moderate” is Grade 4 weakness that does impose functional limitations on the patient, interfering with normal daily activities.
- Note that inability to rise from a chair without assistance constitutes severe glucocorticoid-induced myopathy (Specific Domain)

### **SEVERITY OF GLUCOCORTICOID TOXICITY IN THE SKIN**

Manifestations to be considered:

- Acneiform rash
- Easy bruising
- Hirsutism
- Atrophy/striae
- Erosions/tears/ulcerations

<b>Skin 6b. Mild</b>	<b>Skin 6c. Moderate</b>	<b>Severe (Specific Domain)</b>
Acneiform rash (Grades 1–2)	Acneiform rash (Grade 3)	Acneiform rash (Grade 4)
Easy bruising (Grade 1)	Easy bruising (Grade 2)	
Hirsutism (Grade 1)	Hirsutism (Grade 2)	
Atrophy/striae (Grade 1)	Atrophy/striae (Grade 2)	Atrophy/striae (Grade 3)
Erosions/tears/ulcerations (Grade 1)	Erosions/tears/ulcerations (Grade 2)	Erosions/tears/ulcerations (Grade 3)

## **Appendix 14** **Glucocorticoid Toxicity Change Index (cont.)**

### **Acneiform rash**

- Grade 1: Papules and/or pustules covering <10% body surface area (BSA), which may or may not be associated with symptoms of pruritus or tenderness
- Grade 2: Papules and/or pustules covering 10%–30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental activities of daily living (ADL)
- Grade 3: Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated
- Grade 4: Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with intravenous (IV) antibiotics indicated; life-threatening consequences

### **Easy bruising**

- Grade 1: Localized or in a dependent area
- Grade 2: Generalized

### **Hirsutism: In women, increase in length, thickness, or density of hair in a male distribution**

- Grade 1: Hirsutism that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair
- Grade 2: Hirsutism that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact

### **Atrophy/striae**

- Grade 1: Covering <10% BSA; associated with telangiectasias or changes in skin color
- Grade 2: Covering 10%–30% BSA; associated with striae or adnexal structure loss
- Grade 3: Covering >30% BSA; associated with ulceration

### **Erosions/tears/ulcerations**

- Grade 1: Combined area of ulcers <1 cm; non-blanchable erythema of intact skin associated with warmth or erythema
- Grade 2: Combined area of ulcers 1–2 cm; partial thickness skin loss involving skin or subcutaneous fat
- Grade 3: Combined area of ulcers >2 cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia

## Appendix 14 Glucocorticoid Toxicity Change Index (cont.)

### **SEVERITY OF NEUROPSYCHIATRIC GLUCOCORTICOID TOXICITY**

Manifestations to be considered:

- Insomnia
- Mania
- Cognitive impairment
- Depression

<b>7b. Mild—No Functional Impairment</b>	<b>7c. Moderate—Functional Impairment</b>	<b>Severe (Specific Domain)</b>
Insomnia	Insomnia	
Mania (Grade 1)	Mania (Grade 2)	Mania (Grade 3)
Cognitive impairment (Grade 1)	Cognitive impairment (Grade 2)	Cognitive impairment (Grade 3)
Depression (Grade 1)	Depression (Grade 2)	Depression (Grade 3)

### **DEFINITIONS OF SEVERITY WITHIN THE NEUROPSYCHIATRIC DOMAIN**

**Insomnia: Dissatisfaction with sleep quality and difficulty initiating or maintaining sleep or early morning awakening**

- Grade 1: Not associated with functional impairment
- Grade 2: Associated with functional impairment; recorded as moderate toxicity

#### **Mania**

- Grade 1: Slightly or occasionally elevated or irritable mood and 0–1 mild or occasional additional symptoms of inflated self-esteem, decreased need for sleep, increased talkativeness, feeling that thoughts are faster than usual, distractibility, increased activity or agitation, and impulsive actions
- Grade 2: Frequent or moderately elevated or irritable mood and 2–3 mild additional symptoms of inflated self-esteem, decreased need for sleep, increased talkativeness, feeling that thoughts are faster than usual, distractibility, increased activity or agitation, and impulsive actions
- Grade 3: Severe or constantly elevated or irritable mood and 4 or more additional symptoms of inflated self-esteem, decreased need for sleep, increased talkativeness, feeling that thoughts are faster than usual, distractibility, increased activity or agitation, and impulsive actions

## **Appendix 14** **Glucocorticoid Toxicity Change Index (cont.)**

### **Cognitive impairment**

- Grade 1: Minor cognitive complaints, no objective findings on mental status examination (i.e., not apparent to the examiner) that were not present before initiating steroids
- Grade 2: New moderate cognitive deficits that were not present before initiating steroids
- Grade 3: Frank delirium

### **Depression**

- Grade 1: Feeling slightly down or depressed and 0–2 mild or occasional additional symptoms of loss of interest, low energy, guilt, poor concentration, insomnia, restlessness, or change in appetite
- Grade 2: Frequent or moderate feelings of being down or depressed and/or 3–4 symptoms of loss of interest, low energy, guilt, poor concentration, insomnia, restlessness, or change in appetite
- Grade 3: Severe constant feeling of being down or depressed and/or 5 or more symptoms of loss of interest, low energy, guilt, poor concentration, insomnia, restlessness, or change in appetite and/or suicidal thoughts

### **INFECTION NOTES**

- No significant infection: No specific infections or serious infections Grade 3 or greater
- Specific infections: Oral or vaginal candidiasis or zoster infections without postherpetic neuralgia or eye involvement

Grade 3: IV antibiotic, anti-fungal, or anti-viral intervention or hospitalization indicated or radiologic or operative intervention indicated or herpes zoster complicated by postherpetic neuralgia or eye involvement

Grade 4 or 5: Life-threatening consequences; urgent intervention indicated or death from infection (Specific Domain)

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