Official Title:	A Phase III, Randomized, Double Blind, Placebo-Controlled, Multicenter Study to Evaluate The Efficacy and Safety of Obinituzumab in Patients with ISN/RPS 2003 Class III or IV Lupus Nephritis
NCT Number:	NCT04221477
Document Date:	Protocol Version 5: 07-Feb-2024

PROTOCOL

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OBINUTUZUMAB IN PATIENTS WITH ISN/RPS 2003 CLASS III OR IV LUPUS NEPHRITIS**
PROTOCOL NUMBER:	CA41705
VERSION NUMBER:	5
TEST COMPOUND:	Obinutuzumab (RO5072759)
STUDY PHASE	Phase III
REGULATORY AGENCY IDENTIFIERS:	IND Number: 125,054 EudraCT Number: 2019-004034-42 EU CT Number: 2023-503628-22-00 NCT Number: NCT04221477
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocols		
Version	**Date Final**	**Country**	**Version**	**Date Final**
5	See electronic date stamp on the final page of this document.	—	—	—
4	14 March 2023	—	—	—
3	23 April 2021	—	—	—
2	10 March 2020	United Kingdom	2	5 August 2020
1	23 December 2019	—	—	—

PROTOCOL AMENDMENT, VERSION 5:
RATIONALE

Protocol CA41705 has primarily been amended to update the efficacy-evaluable analysis set, in response to health authority feedback on the statistical analysis plan. All changes to the protocol, along with a rationale for each change, are summarized below in order of appearance:

- "Change in Functional Assessment of Chronic Illness Therapy–Fatigue scale from baseline to Week 76" was promoted from supportive secondary efficacy endpoint to key secondary endpoint, to reflect the high relevance of fatigue from a patient's perspective (Sections 2.1.2 and 6.3.2.1).
- Language regarding proportion of patients who achieve complete renal response with successful prednisone taper at Week 76 has been removed, as this language was left in the previous version of the protocol in error (Section 2.1.3).
- Language regarding anti-dsDNA, C3 and C4 collections has been updated to clarify that these collections are not performed at Week 36, a correction made to align with the Schedule of Activities (Section 2.1.3).
- "Estimated glomerular filtration rate (eGFR) slope from Week 12 to Week 76" has been added as an exploratory efficacy objective as a predicter for future risk of end-stage kidney disease (Section 2.1.3).
- The exploratory efficacy objective "Time to onset of confirmed Stage IV or V chronic kidney disease, renal flare, or rescue therapy during blinded treatment" was revised to "Time to LN flare from Week 24", to newly include a lupus nephritis (LN) flare definition (Section 2.1.3).
- "Time to an unfavorable kidney outcome, defined as the first of the following events: treatment failure, serum creatinine doubling, or death" has been added as an exploratory efficacy objective (Section 2.1.3).
- The process for non-emergency unblinding has been clarified (Section 4.2).
- Language regarding influenza (semi-quantitative) antibody titers has been removed, as the laboratory vendor has ceased to offer influenza IgG antibody testing --service (influenza A and influenza B IgG) as of 13 November 2023. This assay was never intended to be used for clinical management, but to assess the effect of obinutuzumab on specific humoral immunity. There are sufficient samples already collected to perform a robust analysis of the data, and other samples for antibody testing will continue to be collected for this purpose (Section 4.5.5; Appendix 1 [Tables 1–4]).
- Language has been added to clarify that the definition of hepatitis B virus reactivation can be found in the obinutuzumab autoimmune Investigator's Brochure (Section 5.1.3.3 [Table 5]).
- Language has been added to further clarify adverse events of special interest (AESIs) for blinded/open label obinutuzumab, in addition to the study level AESIs previously specified (Section 5.2.3).

- It has been made explicit that expedited safety reports are notified to EudraVigilance (Section 5.7).
- Efficacy-evaluable analysis set has been updated to include all randomized patients regardless of whether they received study treatment, in response to health authority feedback on the statistical analysis plan (Sections 6 and 6.3).
- Intercurrent events of the primary endpoint have been updated, in response to health authority feedback on the statistical analysis plan. Study treatment discontinuation has been added as an intercurrent event that will be handled with treatment policy strategy; death has been specified as an intercurrent event (Section 6.3.1).
- Language has been added to clarify that an interval of 14 days should be kept between paired blinded obinutuzumab infusions to increase standardization of obinutuzumab exposure and decrease variability, and to avoid protocol deviations in situations where infusion visits are delayed for adverse event management There are no safety concerns if the delay time between the two visits was reduced after a delayed initial infusion of paired infusion visits and the 14 day interval was not maintained (Appendix 1 [Tables 1 and 3]).
- Footnotes have been added to clarify that the 24-hour urine collection at the blinded treatment Week 80 visit and open-label Week 0 visit is only required if the Week 76 24-hour urine collection was missing or could not be analyzed, as these were omitted from the previous version in error. Subsequent footnotes have been reordered accordingly (Appendix 1 [Tables 2 and 3]).

Additional minor changes have been made to improve clarity and consistency. Revised text appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OBINUTUZUMAB IN PATIENTS WITH ISN/RPS 2003 CLASS III OR IV LUPUS NEPHRITIS**
PROTOCOL NUMBER:	CA41705
VERSION NUMBER:	5
TEST COMPOUND:	Obinutuzumab (RO5072759)
SPONSOR NAME:	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 of the signed form as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OBINUTUZUMAB IN PATIENTS WITH ISN/RPS 2003 CLASS III OR IV LUPUS NEPHRITIS**
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 125,054 EudraCT Number: 2019-004034-42 EU CT Number: 2023-503628-22-00 NCT Number: NCT04221477

STUDY RATIONALE

The purpose of this study is to evaluate the efficacy, safety, and pharmacokinetics of obinutuzumab compared with placebo in patients with International Society of Nephrology/Renal Pathology Society (ISN/RPS) Class III or IV lupus nephritis (LN) when added on to standard-of-care therapy consisting of mycophenolate mofetil (MMF) and corticosteroids.

OBJECTIVES AND ENDPOINTS

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of obinutuzumab (combined treatment groups) compared with placebo	• Proportion of patients who achieve a CRR at Week 76 CRR is defined as achievement of all of the following: – UPCR < 0.5 g/g – eGFR ≥ 85% of baseline, as calculated using the CKD-EPI equation – No occurrence of *the following* intercurrent events: Rescue therapy, treatment failure, *death or* early study withdrawal

ADA = anti-drug antibody; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CRR = complete renal response; eGFR = estimated glomerular filtration rate; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; IRR = infusion-related reaction; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = overall renal response; PK = pharmacokinetic; PRR = partial renal response; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; ULN = upper limit of normal; UPCR = urinary protein-to-creatinine ratio.

Objectives and Endpoints (cont.)

Secondary Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of obinutuzumab (combined treatment groups) compared with placebo	Key secondary endpoints: • Proportion of patients who achieve a proteinuric response at Week 76 Proteinuric response is defined as achievement of all of the following: – UPCR < 0.8 g/g – No occurrence of *the following* intercurrent events: Rescue therapy, treatment failure, *death or* early study withdrawal • Proportion of patients who achieve CRR with successful prednisone taper at Week 76, defined as achievement of CRR (as above) at Week 76 with the following: – No receipt of prednisone > 7.5 mg/day (or equivalent) from Week 64 through Week 76 • Proportion of patients who achieve an ORR, defined as achievement of either CRR or PRR, evaluated at Week 50 PRR is defined as achievement of <u>all</u> of the following: – ≥ 50% reduction in UPCR from baseline – UPCR < 1 g/g (or < 3 g/g if the baseline UPCR was ≥ 3 g/g) – eGFR ≥ 85% of baseline, as calculated using the CKD-EPI equation – No occurrence of *the following* intercurrent events: Rescue therapy, treatment failure, *death or* early study withdrawal • Proportion of patients who experience death or renal-related events through Week 76, defined as the proportion of patients with one or more of the following events: – Death – Treatment failure – Worsening proteinuria, defined as a confirmed ≥ 50% increase in UPCR to a value ≥ 3 – Worsening eGFR, define as a confirmed ≥ 30% decrease in eGFR to a value < 60 • Mean change in eGFR from baseline to Week 76 • *Change in FACIT-F scale from baseline to Week 76*

ADA = anti-drug antibody; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CRR = complete renal response; eGFR = estimated glomerular filtration rate; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; IRR = infusion-related reaction; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = overall renal response; PK = pharmacokinetic; PRR = partial renal response; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; ULN = upper limit of normal; UPCR = urinary protein-to-creatinine ratio.

Objectives and Endpoints (cont.)

Secondary Efficacy Objective	Corresponding Endpoints
To evaluate the efficacy of obinutuzumab (combined treatment groups) compared with placebo	Supportive Secondary Endpoints: • Change in anti-dsDNA titer from baseline to Week 50 • Change in C3 from baseline to Week 50 • Change in SLEDAI-2K from baseline to Week 76 • Time to onset of CRR over the course of 76 weeks • Proportion of patients who achieve CRR with serum creatinine criteria at Week 76 CRR with serum creatinine criteria is defined as achievement of all of the following: – UPCR $<$ 0.5 g/g – Serum creatinine $\leq$ ULN (as determined by the central laboratory) – Serum creatinine not increased from baseline by $>$ 25% – No occurrence of *the following* intercurrent events: Rescue therapy, treatment failure, *death or* early study withdrawal
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of obinutuzumab (combined treatment groups) compared with placebo	• Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0 • Characterization of adverse events of special interest, including, among others, IRRs, neutropenia, infections, and thrombocytopenia • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
PK Objective	**Corresponding Endpoint**
• To characterize the obinutuzumab PK profile	• Serum concentration of obinutuzumab at specified timepoints

ADA = anti-drug antibody; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CRR = complete renal response; eGFR = estimated glomerular filtration rate; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; IRR = infusion-related reaction; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = overall renal response; PK = pharmacokinetic; PRR = partial renal response; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; ULN = upper limit of normal; UPCR = urinary protein-to-creatinine ratio.

Objectives and Endpoints (cont.)

Immunogenicity Objective	Corresponding Endpoint
• To evaluate the immune response to obinutuzumab on the basis of the following endpoint	• Prevalence of ADAs at baseline and incidence of ADAs posttreatment during the study (only for patients treated with obinutuzumab)
Biomarker Objective	**Corresponding Endpoint**
• To characterize the obinutuzumab-induced changes in circulating B cells	• Total peripheral B-cell count at specified timepoints

ADA = anti-drug antibody; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CRR = complete renal response; eGFR = estimated glomerular filtration rate; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; IRR = infusion-related reaction; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; ORR = overall renal response; PK = pharmacokinetic; PRR = partial renal response; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; ULN = upper limit of normal; UPCR = urinary protein-to-creatinine ratio.

OVERALL DESIGN AND STUDY POPULATION

This parallel-group, double-blind, randomized, placebo-controlled study will compare the efficacy and safety of obinutuzumab versus placebo among patients with ISN/RPS 2003 Class III or IV LN treated with standard-of-care therapy with MMF and corticosteroids.

Several key aspects of the study design and study population are summarized below.

Phase:	Phase III	**Population Type:**	Adult patients
Control Method:	Placebo	**Population Diagnosis or Condition:**	Active or active/chronic ISN/RPS Class III or IV proliferative LN
Interventional Model:	Parallel group	**Population Age:**	18–75 years
Test Compound{s}:	Obinutuzumab	**Site Distribution:**	Multi-site and multi-region
Active Comparator:	Not Applicable	**Study Intervention Assignment Method:**	Randomization
Number of Arms:	2	**Number of Participants to Be Enrolled:**	Approximately 252

STUDY TREATMENT

Obinutuzumab 1000 mg or placebo will be administered by IV infusion during blinded treatment at Day 1 and Weeks 2, 24, 26, 50, and 52. Subsequent blinded infusions will occur at Week 80 and every 6 months thereafter for patients with an adequate response at Week 76. Open-label treatment (OLT) will follow the initial obinutuzumab treatment schedule with infusions on OLT Day 1; at OLT Weeks 2, 24, 26, 52 and every 6 months thereafter.

All patients will receive MMF from the baseline visit (Day 1) onward. MMF will be titrated by Week 4 to a target dose of 2.0–2.5 g/day in divided doses. For patients newly initiating MMF,

the recommended initial dosage is 1.5 g/day given in divided doses with titration by 500 mg/week to 2.0–2.5 g/day by Week 4.

MMF should be maintained at the target dose through Week 80. Adjustments to MMF dosing will be permitted because of intolerance and adverse events. The dosage should not exceed 2.5 g/day unless discussed with the Medical Monitor.

After Week 80, MMF may be adjusted or switched to azathioprine at the discretion of the investigator.

During the 6 months prior to screening, during screening, or on Day 1 (prior to the first infusion), all patients must have received at least one dose of pulse-dose methylprednisolone IV (250–1000 mg) or equivalent for the treatment of the current episode of active LN. Where possible, pulse corticosteroids should be completed prior to screening. The maximum permitted dose of pulse corticosteroids during the 4 weeks prior to screening or during screening is 3 g methylprednisolone IV or equivalent. If not given during the 6 months prior to screening or during screening, a single dose of pulse-dose methylprednisolone IV (250–1000 mg) will be given in place of pre-infusion methylprednisolone 80 mg IV on Day 1 only.

On Day 2, all patients will receive oral prednisone 0.5 mg/kg/day (maximum 60 mg/day) and remain at this dose until the Week 2 visit. Beginning on Day 15, prednisone will be tapered to achieve a target dose of 5 mg/day by Week 24. Prednisone will be maintained at 5 mg/day from Week 24 until Week 80.

After Week 80, doses of corticosteroids may be adjusted at the discretion of the investigator.

Methylprednisolone 80 mg IV, acetaminophen (650–1000 mg) orally (PO), and diphenhydramine 50 mg PO or IV (or equivalent dose of a similar agent) will all be administered as premedication for study treatment infusions.

For blinded infusions at Week 80 and beyond, premedication with methylprednisolone will only be given to those patients who experienced an infusion-related reaction (IRR) with the previous blinded infusion. Acetaminophen and diphenhydramine will be administered prior to all infusions.

During OLT, all patients will receive premedication with methylprednisolone 80 mg IV through the OLT Week 52 infusion; subsequently, pre-infusion methylprednisolone will only be given to patients who experienced an IRR with the previous obinutuzumab infusion. Acetaminophen and diphenhydramine will be administered prior to all infusions.

Duration of Participation

The end of this study is defined as the date when the last patient, last visit (LPLV), occurs or the date at which study follow-up (SFU) is received from the last patient up to a maximum of 18 months from the last obinutuzumab infusion (blinded and open-label). The end of the study is expected to occur approximately 5 years after the last patient is enrolled.

COMMITTEES

Independent Committees:	Independent Data Monitoring Committee
Other Committees:	Not applicable

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACE	angiotensin-converting enzyme
ACR	American College of Rheumatology
ADA	anti-drug antibody
ANA	antinuclear antibody
ARB	angiotensin-receptor blocker
AUC	area under the concentration-time curve
BCG	Bacillus Calmette-Guérin
BILAG	British Isles Lupus Assessment Group
BTK	Bruton's tyrosine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
ClinRO	clinician-reported outcome
CLL	chronic lymphocytic leukemia
CMH	Cochrane-Mantel-Haenszel
CRR	complete renal response
DIC	disseminated intravascular coagulation
DRB	Data Review Board
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EQ-5D-5L	EuroQol 5-Dimension, 5-Level Questionnaire
ESRD	end-stage renal disease
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy–Fatigue
FDA	Food and Drug Administration
FL	follicular lymphoma
FMV	first morning void
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	health-related quality of life
HSFC	high-sensitivity flow cytometry
ICH	International Council for Harmonisation
iDCC	independent Data Coordinating Center

Abbreviation	Definition
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRR	infusion-related reaction
ISN	International Society of Nephrology
IVIG	intravenous immunoglobulin
IxRS	interactive Web response system
JAK	Janus-associated kinase
KDIGO	Kidney Disease: Improving Global Outcomes
LN	lupus nephritis
LPLV	last patient, last visit
LUNAR	Study U2970g; a Phase III, randomized, double-blind, placebo-controlled, multicenter study of rituximab in LN
MMF	mycophenolate mofetil
MN	mobile nursing
MPA	mycophenolic acid
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NHL	non-Hodgkin lymphoma
NK	natural killer
NOBILITY	Study WA29748; a Phase II randomized, double-blind, placebo-controlled, multicenter study of obinutuzumab in LN
NSAID	non-steroidal anti-inflammatory drug
OLT	open-label treatment
ORR	overall renal response
PD	pharmacodynamic
PGA	Physician's Global Assessment
PK	Pharmacokinetic
PO	Orally
PML	progressive multifocal leukoencephalopathy
PRO	patient-reported outcome
PRR	partial renal response
RBR	Research Biosample Repository
RPS	Renal Pathology Society
SF-36 v2	36-Item Short Form Survey, Version 2
SFU	study follow-up

Abbreviation	Definition
SGA	Subject's Global Assessment
SLE	systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
TB	Tuberculosis
THEORY	Study WT29749; a Phase Ib, open-label study of obinutuzumab in highly sensitized individuals with ESRD awaiting kidney transplantation
TYK2	tyrosine kinase 2
ULN	upper limit of normal
UPCR	urinary protein-to-creatinine ratio
VAS	Visual Analog Scale
WES	whole exome sequencing
WGS	whole genome sequencing

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 unmet medical need in SLE is high. Most patients with moderate or severe disease receive off-label treatment with immunosuppressives including corticosteroids, mycophenolic acid (MPA) (as either mycophenolate mofetil [MMF] or Myfortic® [MPA as sodium salt]), azathioprine, and/or cyclophosphamide. 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 the most common organ-threatening manifestation of SLE and remains a major cause of morbidity and mortality among patients with SLE. The presence of biopsy-proven proliferative nephritis, defined as International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) 2003 Class III or IV LN, is associated with a high risk of progression to end-stage renal disease (ESRD), even with treatment. Current standard-of-care therapy for patients with proliferative LN includes use of corticosteroids in combination with either MMF or cyclophosphamide (Hahn et al. 2012; Bertsias et al. 2012; Fanouriakis et al. 2019). Despite use of these therapies, a minority of patients achieve a complete response within the first 1–2 years, and the rate of progression to ESRD has not decreased in recent decades (Tektonidou et al. 2016). In addition, these standard-of-care therapies are also associated with substantial toxicities that contribute to the morbidity associated with LN. Given the seriousness of this condition, the limited efficacy of current standard of care, and the toxicities associated with current standard of care, there remains a high need for new safe and effective therapies for the treatment of proliferative LN.

1.2 BACKGROUND ON OBINUTUZUMAB

Obinutuzumab (GAZYVA®, GAZYVARO®) 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).

Obinutuzumab is currently approved in multiple countries worldwide for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL) in combination with chlorambucil; for the treatment (in combination with chemotherapy followed by monotherapy in patients achieving at least a partial remission) of adult patients with previously untreated stage II bulky, III or IV follicular lymphoma (FL); and for the

treatment (in combination with bendamustine followed by monotherapy) of patients with FL who relapsed after, or are refractory to, a rituximab-containing regimen.

Compared with type I anti-CD20 antibodies, obinutuzumab has greater antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis, has more direct B-cell–killing effects, and is less reliant on complement-dependent cytotoxicity (Mössner et al. 2010). Because obinutuzumab does not elicit CD20 redistribution to membrane-bound lipid rafts, obinutuzumab is also associated with reduced internalization (Reddy et al. 2017). Glycoengineering of the Fc portion of obinutuzumab results in a higher affinity for FcγRIII receptors on immune effector cells such as natural killer (NK) cells and macrophages/monocytes (Mössner et al. 2010).

Obinutuzumab depletes peripheral and tissue B-cells to a greater degree than rituximab, as evidenced by data in non-human primates (Mössner et al. 2010) and lupus-prone mouse models (unpublished Roche data). Obinutuzumab demonstrated greater in vitro B-cell cytotoxicity and activation of NK cells than rituximab in rheumatoid arthritis and SLE patient blood samples (Reddy et al. 2017). In the Phase II Study WA29748 (NOBILITY), obinutuzumab resulted in rapid and complete peripheral B-cell depletion in LN patients to a greater extent than observed with rituximab in the Phase III Study U2970g (LUNAR).

The safety of obinutuzumab has been evaluated in clinical studies in oncology and non-oncology indications (see Obinutuzumab Immunology Investigator's Brochure). These include oncology patients with CLL or non-Hodgkin lymphoma (NHL) following obinutuzumab doses of 50–2000 mg, primarily in combination with chemotherapy. Data from non-oncology patients are derived from patients with LN where obinutuzumab was given in combination with MMF and corticosteroids and patients with ESRD where obinutuzumab administration was followed by high-dose intravenous immunoglobulin (IVIG).

The efficacy of obinutuzumab in non-oncology patient populations has been studied in patients with LN (NOBILITY) and in an exploratory study in patients with ESRD (Study WT29749 [THEORY]). NOBILITY, a Phase II, double-blinded, randomized, placebo-controlled study comparing the efficacy and safety of obinutuzumab plus MMF/MPA (obinutuzumab group) with placebo plus MMF/MPA (control group) in ISN/RPS 2003 Class III and IV patients with proliferative LN met its primary and key secondary efficacy endpoints (see Section 1.3). THEORY was a Phase Ib, open-label study in highly sensitized individuals with ESRD awaiting kidney transplantation. The effect of obinutuzumab in combination with IVIG on anti–human leukocyte antigen allosensitization was limited and not clinically meaningful for most patients.

In summary, obinutuzumab is a humanized, glycoengineered Type II anti-CD20 antibody with enhanced depletion of B-cells from peripheral blood and tissue compared with Type I antibodies such as rituximab and ofatumumab. Consistent with its more potent

B-cell depletion, obinutuzumab was superior to rituximab for the treatment of CLL and FL when administered in combination with standard chemotherapy and is currently approved worldwide in these indications. Obinutuzumab demonstrated rapid and complete peripheral B-cell depletion in LN patients in NOBILITY and was associated with a clinically meaningful benefit on the achievement of complete renal response (CRR).

Refer to the Obinutuzumab Immunology Investigator's Brochure for additional details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

B cells play a key role and serve multiple functions in the disease pathogenesis through autoantibodies, immune complexes, and amplifying activation of adaptive immune responses (Foster 2007). However, in randomized clinical trials, the Type I anti-CD20 antibodies rituximab and ocrelizumab failed to increase the rate of CRR in proliferative LN (Rovin et al. 2012; Mysler et al. 2013). Incomplete B-cell depletion following rituximab administration is common in lupus patients, and the degree of B-cell depletion following rituximab may be associated with clinical response (Vital et al. 2011; Gomez Mendez et al. 2018). In addition, nonclinical studies have demonstrated that lupus-prone mice have shown resistance to B-cell depletion by anti-CD20 antibodies due to interference in Fc receptor mediated phagocytosis of opsonized cells by lupus serum (Ahuja et al. 2007, 2011).

These lines of evidence provided a scientific rationale to support the Phase II evaluation of obinutuzumab in patients with LN with the hypothesis that greater B-cell depletion would increase response rates above those observed with Type I anti-CD20 monoclonal antibodies such as rituximab or ocrelizumab (Rovin et. al. 2012; Mysler et al. 2013). NOBILITY, a Phase II randomized, double-blind, placebo-controlled, multicenter study, was therefore conducted to evaluate the safety and efficacy of obinutuzumab or placebo infusions at Weeks 0, 2, 24, and 26 in patients with ISN/RPS 2003 Class III or IV proliferative LN treated with MMF and a corticosteroid taper.

NOBILITY met its primary endpoint with a statistically significant difference in CRR between the two treatment groups at Week 52 at a pre-specified two-sided α level of 0.2. At Week 52, 35% of patients in the obinutuzumab group and 23% of patients in the control group achieved CRR (+12% difference; 80% CI: 2.1%, 23%]; $p = 0.115$). At Week 52, key secondary efficacy endpoints were also met including overall renal response (ORR), defined as obtaining either a complete or partial renal response (PRR), achieved by 56% of patients in the obinutuzumab group and 36% of patients in the control group (+20% difference; 80% CI: [8.9% to 31%]; $p = 0.025$), CRR excluding urinary sediment, and clinically meaningful improvements in serologic markers of lupus disease activity including anti-dsDNA antibody titer, C3, and C4. An exploratory analysis of the Week 76 efficacy data demonstrated an increasing treatment benefit of

obinutuzumab over control beyond Week 52 (CRR: obinutuzumab 40% vs. control 17%, +22% difference; $p = 0.007$).

Obinutuzumab was associated with rapid and complete depletion of peripheral B cells in NOBILITY. At Week 2, 88% of obinutuzumab patients had peripheral B cells depleted below the limit of quantitation of a high-sensitivity flow cytometry (HSFC) assay ($\leq$0.441 cells/μL). The NOBILITY regimen resulted in continued B-cell depletion through Week 52, at which point 80% of obinutuzumab patients were depleted to $\leq$0.441 cells/μL. Peripheral B-cell repletion had occurred for the majority of patients by the next measurement at Week 104; only 8% of obinutuzumab patients remained depleted at Week 104. Among obinutuzumab-treated patients, achievement of sustained B-cell depletion through Week 52 was associated with increased renal response.

At the NOBILITY Week 76 data cut, obinutuzumab was not associated with increased serious adverse events (23% of obinutuzumab patients vs. 30% of placebo patients experienced at least one serious adverse event), serious infections (6% vs. 18% incidence), or deaths (2% vs. 7% incidence) compared with placebo. Obinutuzumab was associated with increased non-serious infusion-related reactions (IRRs; 16% vs. 10%). There were no serious IRRs in either group, and no IRRs resulted in the inability to complete the obinutuzumab infusion (following protocol-instructed management, which may have included interruption or slowing of the infusion). No new safety signals were identified.

The Sponsor interprets the efficacy and safety of obinutuzumab in combination with MMF and corticosteroids observed in NOBILITY as being clinically meaningful for the treatment of LN. The current study (CA41705) is being undertaken to confirm the results of NOBILITY and provide long-term data to inform the use of obinutuzumab in proliferative LN.

Given the associations between sustained B-cell depletion and response, and the return of peripheral B-cells observed at Week 104 in NOBILITY, obinutuzumab will be administered in the current study (CA41705) at Day 1 and Weeks 2, 24, 26, and again at 12 months (either Weeks 50 and 52 or Week 52 only), and every 6 months thereafter for patients with an adequate response to treatment, in order to maintain B-cell depletion and increase the degree and durability of clinical benefit with obinutuzumab.

COVID-19 Benefit–Risk Assessment

An assessment was conducted to determine whether there is any impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit–risk assessment of this study protocol including, but not limited to, the patient population under study and study treatments being evaluated. Based on that assessment, no impact is anticipated, and the existing safety monitoring and management guidelines and risk-mitigation measures provided in the study protocol are considered adequate.

With reference to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, the coronavirus strain that causes COVID-19) vaccines, an assessment was conducted to determine whether there is any impact of the SARS-CoV-2 vaccines on the benefit-risk assessment of this study protocol. Given the mechanism of action of obinutuzumab, it is expected that the efficacy of SARS-CoV-2 vaccines may be diminished in patients who are B-cell depleted. The investigator should use clinical judgement to decide on the most suitable timing of vaccination and, where possible, SARS-CoV-2 vaccines should be administered to patients before they start immunosuppressive therapy. The SARS-CoV-2 vaccines may also be administered at any time during the study provided they are non-live vaccines. If administered during the study, the SARS-CoV-2 vaccines are considered concomitant medications. The SARS-CoV-2 vaccines must be administered in accordance with the approved/authorized vaccine label (or equivalent) and official immunization instructions. Based on this assessment, no additional risk mitigation measures related to SARS-CoV-2 vaccination are proposed at this time. The recommendations listed above and the current safety monitoring and management guidelines and risk-mitigation measures provided in the study protocol are considered adequate.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of obinutuzumab compared with placebo in patients with ISN/RPS Class III or IV LN when added on to standard-of-care therapy consisting of MMF and corticosteroids. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of obinutuzumab (combined treatment groups) compared with placebo on the basis of the following endpoint:

- Proportion of patients who achieve a complete renal response (CRR) at Week 76

  CRR is defined as achievement of all of the following:

  - Urinary protein-to-creatinine ratio (UPCR) <0.5 g/g
  - Estimated glomerular filtration rate (eGFR) $\geq 85\%$ of baseline, as calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation
  - No occurrence of *the following* intercurrent events:
    - Rescue therapy, treatment failure, *death or* early study withdrawal

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of obinutuzumab (combined treatment groups) compared with placebo on the basis of the following endpoints.

Key Secondary Endpoints

- Proportion of patients who achieve a proteinuric response at Week 76

  Proteinuric response is defined as achievement of all of the following:

  - UPCR < 0.8 g/g
  - No occurrence of *the following* intercurrent events:
    - Rescue therapy, treatment failure, *death or* early study withdrawal
- Proportion of patients who achieve CRR with successful prednisone taper at Week 76, defined as achievement of CRR (as above) at Week 76 with the following:
  - No receipt of prednisone > 7.5 mg/day (or equivalent) from Week 64 through Week 76
- Proportion of patients who achieve an overall renal response (ORR), defined as achievement of either CRR or partial renal response (PRR), evaluated at Week 50

  PRR is defined as achievement of <u>all</u> of the following:

  - ≥50% reduction in UPCR from baseline
  - UPCR <1 g/g (or <3 g/g if the baseline UPCR was ≥3 g/g)
  - eGFR ≥ 85% of baseline, as calculated using the CKD-EPI equation
  - No occurrence of *the following* intercurrent events:
    - Rescue therapy, treatment failure, *death or* early study withdrawal
- Proportion of patients who experience death or renal-related events through Week 76, defined as the proportion of patients with one or more of the following events:
  - Death
  - Treatment failure (see Section 4.4.4.2)
  - Worsening proteinuria, defined as a confirmed ≥50% increase in UPCR to a value ≥3
  - Worsening eGFR, define as a confirmed ≥30% decrease in eGFR to a value <60
- Mean change in eGFR from baseline to Week 76
- *Change in Functional Assessment of Chronic Illness Therapy –Fatigue (FACIT-F) scale from baseline to Week 76*

Supportive Secondary Endpoints

- Change in anti-dsDNA titer from baseline to Week 50

- Change in C3 from baseline to Week 50
- Change in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) from baseline to Week 76
- Time to onset of CRR over the course of 76 weeks
- Proportion of patients who achieve CRR with serum creatinine criteria at Week 76

  CRR with serum creatinine criteria is defined as achievement of <u>all</u> of the following:

  – UPCR $<$0.5 g/g
  – Serum creatinine $\leq$upper limit of normal (ULN) (as determined by the central laboratory)
  – Serum creatinine not increased from baseline by $>$25%
  – No occurrence of *the following* intercurrent events:
    - Rescue therapy, treatment failure, *death or* early study withdrawal

2.1.3 Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of obinutuzumab (combined treatment groups) compared with placebo on the basis of the following endpoints:

- Proportion of patients who achieve the individual components of CRR at Week 76:
  – UPCR $<$0.5 g/g
  – eGFR $\geq$ 85% of baseline, as calculated using the CKD-EPI equation
  – No occurrence of *the following* intercurrent events:
    - *Rescue therapy, treatment failure, death or early study withdrawal*
- Proportion of patients who achieve CRR with successful prednisone taper at Week 76, defined as achievement of CRR (as above) with the following:
  – No receipt of prednisone $>$ 7.5 mg/day (or equivalent) from Week 52 through Week 76
- Proportion of patients who achieve CRR at Weeks 36, 50, and 64
- Proportion of patients who achieve proteinuric response at Weeks 36, 50, and 64
- Proportion of patients who achieve ORR at Weeks 36, 64, and 76
- Proportion of patients who achieve CRR on the randomized, blinded therapy at Weeks 106, 132, 158, 184, and 210
- Proportion of patients who achieve proteinuric response on the randomized, blinded therapy at Weeks 106, 132, 158, 184, and 210
- Proportion of patients who achieve ORR on the randomized, blinded therapy at Weeks 106, 132, 158, 184, and 210

- Proportion of patients who achieve CRR with serum creatinine ≤ ULN at Week 76, as defined as achievement of all of the following:
  - UPCR < 0.5 g/g
  - Serum creatinine ≤ ULN (as determined by the central laboratory)
  - No occurrence of *the following* intercurrent events:
    - *Rescue therapy, treatment failure, death or early study withdrawal*
- *Proportion of patients who achieve CRR at Week 76, as defined as achievement of all of the following:*
  - *UPCR < 0.5 g/g*
  - *eGFR ≥ 85% of baseline, as calculated using the CKD-EPI equation or ≥ 60 mL/min per 1.73 mL² of body-surface area*
  - *No occurrence of the following intercurrent events:*
    - *Rescue therapy, treatment failure, death or early study withdrawal*
- Proportion of patients who achieve the CRR serum creatinine criteria at Week 76

  The CRR serum creatinine criteria require achievement of all of the following:
  - Serum creatinine ≤ ULN (as determined by the central laboratory)
  - Serum creatinine not increased from baseline by > 25%
  - No occurrence of *the following* intercurrent events:
    - *Rescue therapy, treatment failure, death or early study withdrawal*
- Proportion of patients who receive rescue therapy or experience treatment failure by Week 76
- Change in anti-dsDNA titer from baseline to Weeks 4, 12, 24, and 76
- Change in C3 from baseline to Weeks 4, 12, 24, and 76
- Change in C4 from baseline to Weeks 4, 12, 24, 50, and 76
- Change in UPCR from baseline to Weeks 24, 50, and 76
- *eGFR slope from Week 12 to Week 76*
- Time from first CRR to loss of any response, defined as a failure to meet criteria for either CRR or PRR, during blinded treatment
- *Time to LN flare from Week 24, diagnosed if one of the following conditions occurred:*
  - *eGFR decrease > 20% compared with Week 24 in patients with UPCR > 1 g/g and/or cellular casts;*
  - *UPCR increase (i) to > 1 g/g if Week 24 UPCR was < 0.2 g/g, (ii) to > 2.0 g/g if Week 24 UPCR was 0.2–1 g/g, or (iii) to doubling if Week 24 UPCR was > 1 g/g; or*
  - *receipt of rescue therapy, except for corticosteroid-only rescue.*

- *Time to an unfavorable kidney outcome, defined as the first of the following events: treatment failure, serum creatinine doubling, or death*
- Proportion of patients who achieve CRR including urinary sediment at Week 76, defined as achievement of CRR (as above) with urinary RBCs < 10 per high-power field (HPF) without RBC casts
- Cumulative corticosteroid dose from baseline to Week 76
- Change in health-related quality of life (HRQoL) as measured by the 36-Item Short Form Survey, Version 2 (SF-36 v2) from baseline to Week 76
- Change in Physician's Global Assessment (PGA) from baseline to Weeks 24, 50, and 76
- Change in Subject's Global Assessment (SGA) from baseline to Weeks 24, 50, and 76

Additionally, descriptive comparisons of the obinutuzumab treatment groups will be performed on the basis of the renal response endpoints described above.

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety of obinutuzumab (combined treatment groups) compared with placebo on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0
- Characterization of adverse events of special interest, including, among others, IRRs, neutropenia, infections, and thrombocytopenia
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

2.3 PHARMACOKINETIC OBJECTIVE

The pharmacokinetic (PK) objective for this study is to characterize the obinutuzumab PK profile on the basis of the following endpoint:

- Serum concentration of obinutuzumab at specified timepoints

2.4 IMMUNOGENICITY OBJECTIVES

The immunogenicity objective for this study is to evaluate the immune response to obinutuzumab on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs post-treatment during the study (only for patients treated with obinutuzumab)

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following measures:

- Relationship between ADA status and efficacy, safety, pharmacodynamic (PD), or PK endpoints

2.5 BIOMARKER OBJECTIVE

The PD objective for this study is to characterize the obinutuzumab-induced changes in circulating B-cells based on the following endpoint:

- Total peripheral B-cell count at specified timepoints

2.6 HEALTH STATUS UTILITY OBJECTIVE

The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with obinutuzumab on the basis of the following endpoints:

- Change from baseline in EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) index-based and Visual Analog Scale (VAS) scores at Weeks 0, 24, 50, and 76

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a parallel-group, double-blind, randomized, placebo-controlled study comparing the efficacy and safety of obinutuzumab versus placebo among patients with ISN/RPS 2003 Class III or IV LN treated with standard-of-care therapy with MMF and corticosteroids. The study will enroll approximately 252 patients.

Patients must be 18–75 years of age and have active or active/chronic ISN/RPS Class III or IV proliferative LN as evidenced by renal biopsy performed in the 6 months prior to screening or during screening. Patients may have concomitant Class V disease (i.e., Class III/V or Class IV/V). Patients must exhibit significant proteinuria as evidenced by a UPCR $\geq$ 1 g/g based on a 24-hour urine collection during screening.

Key exclusion criteria include evidence of severe renal impairment, defined by an eGFR $<$ 30 mL/min per 1.73 m^2 of body surface area or ESRD requiring dialysis or transplantation; evidence of active infection; and other safety-related exclusions.

The study consists of the following study periods: screening, blinded treatment, open-label treatment (OLT), and study follow-up (SFU).

3.1.1 Screening

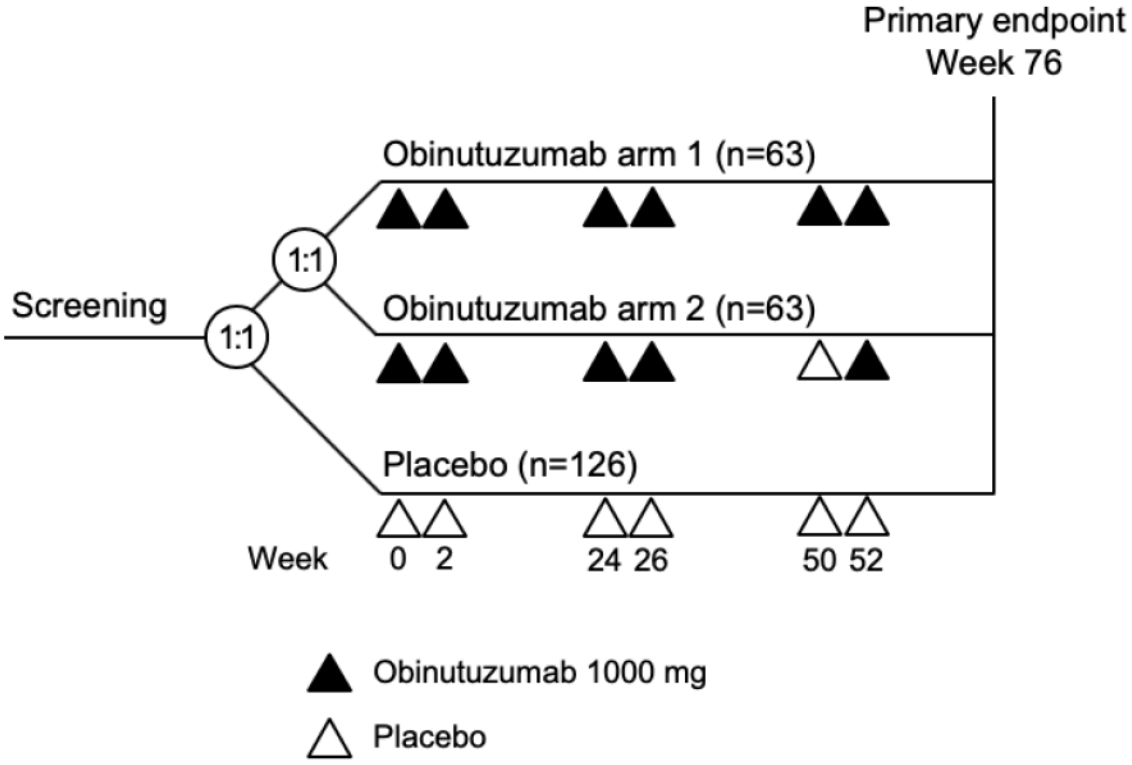
Consenting patients will enter a screening period of up to 28 days to be evaluated for eligibility. Procedures at screening will include collecting a medical history, a full physical examination, ECG, and blood and urine sampling. Patients without a renal biopsy within the 6 months prior to screening must undergo a renal biopsy during the screening period.

3.1.2 Blinded Treatment

Randomized patients will receive blinded infusions of obinutuzumab 1000 mg or placebo on Day 1 and Weeks 2, 24, 26, 50, and 52 in three treatment groups according to

Figure 1 below. All patients will receive MMF (see Section 4.3.1.2) and corticosteroids (see Section 4.3.2.1). The primary endpoint, CRR, will be assessed at Week 76. Patients will be offered an optional renal biopsy following the Week 76 assessment (see Section 4.5.9).

Figure 1 Study Schema



MMF = mycophenolate mofetil.

Eligibility for subsequent infusions after Week 76 will be determined based on the investigator's assessment of the adequacy of treatment response, need for intensification of therapy, and presence of unmanageable treatment-emergent adverse events according to the guidance provided in Table 1. The randomized treatment assignment will not be revealed during this process and investigators and patients will remain blinded until study unblinding occurs (see Section 3.1.5).

Table 1 Study Treatment after Week 76

Week 76 Response	Clinical Criteria, as Assessed by the Investigator	Subsequent Treatment
Adequate response	– Adequate response to treatment and – No need for intensification of therapy and – No unmanageable treatment-emergent adverse events	Continue blinded infusions every 6 months
Inadequate response with some improvement from baseline	– Inadequate response to treatment and – Clinically meaningful improvement from baseline in renal parameters or prior clinically meaningful improvement followed by worsening and – Current need for intensification of therapy and – No unmanageable treatment-emergent adverse events	Open-label treatment (see Section 3.1.3)
All others	– Primary nonresponse: no clinically meaningful improvement at any time or – Early discontinuation of blinded infusions or – Receipt of rescue therapy [a] or treatment failure or – Unmanageable treatment-emergent adverse events	Study follow-up (see Section 3.1.4) and treatment with standard of care at the investigator's discretion

[a] Except corticosteroid-only rescue (see Section 4.4.4.1).

Patients who have an adequate response at Week 76 without a need for intensification of therapy or unmanageable treatment-emergent adverse events will continue to receive blinded obinutuzumab 1000 mg or placebo infusions every 6 months beginning at Week 80. Background immunosuppression, including doses of corticosteroids and MMF, will be adjusted at the investigator's discretion beginning at Week 80.

An adequate response is present if all of the following criteria are met:

- UPCR $<$ 0.8 g/g or $\geq$ 50% reduction in UPCR from baseline to subnephrotic levels ($<$ 3 g/g)
- No deterioration in renal function from baseline (eGFR $\geq$ 85% of baseline)
- No need for high-dose corticosteroids
- No receipt of rescue therapy or treatment failure

Investigators may discuss the adequacy of response and appropriateness of continuing blinded treatment directly with the Medical Monitor if needed.

During continued blinded treatment, investigators should regularly review the study safety plan (see Section 5.1), including the risks associated with obinutuzumab (see Section 5.1.1) and management of specific adverse events that may be related to obinutuzumab (see Section 5.1.3.3), to ensure the patient has not developed a condition that would warrant discontinuation of blinded infusions. Prior to resuming blinded treatment after treatment interruption, investigators should refer to Section 5.1.3.2 to ensure the patient meets the criteria for resuming treatment.

After study unblinding (see Section 3.1.5), no further blinded infusions will be provided through the study protocol. Subsequent access to obinutuzumab may occur through post-trial access (see Section 4.3.4).

After Week 80, patients who, in the opinion of the investigator, experience a loss of response and require intensification of therapy during blinded treatment may be eligible to receive OLT (see Section 3.1.3).

Patients who discontinue blinded infusions and do not enter OLT will enter SFU (see Section 3.1.4).

3.1.3 Open-Label Treatment

For patients with an inadequate treatment response at Week 76, open-label treatment with obinutuzumab will be provided if all of the following criteria are met at Week 76:

- Inadequate treatment response
- Clinically meaningful improvement from baseline in renal parameters or prior clinically meaningful improvement from baseline followed by worsening
- Need for intensification of therapy
- No unmanageable treatment-emergent adverse events
- No rescue therapy (except corticosteroid-only rescue; see Section 4.4.4.1.1) or treatment failure

Documentation of these criteria will be submitted to the Medical Monitor for review. Investigators may discuss the appropriateness of OLT directly with the Medical Monitor if needed. For patients who initiate OLT based on the Week 76 assessment, the first OLT visit (OLT Day 1) will occur on Week 80.

Additionally, patients who, during blinded treatment after Week 80, experience a loss of adequate response requiring intensification of therapy and without unmanageable treatment-emergent adverse events may initiate OLT once 60 days have elapsed from the most recent obinutuzumab or placebo infusion.

During OLT, patients will receive obinutuzumab 1000 mg on OLT Day 1 and OLT Weeks 2, 24, 26, 52, and once every 6 months thereafter. Background immunosuppression, including doses of corticosteroids and MMF, may be adjusted at the investigator's discretion beginning at OLT Day 1.

During OLT, investigators should regularly review the study safety plan (see Section 5.1), including the risks associated with obinutuzumab (see Section 5.1.1) and management of specific adverse events that may be related to obinutuzumab (see Section 5.1.3.3), to ensure the patient has not developed a condition that would warrant discontinuation of obinutuzumab infusions. Prior to resuming OLT after treatment

interruption, investigators should refer to Section 5.1.3.2 to ensure the patient meets the criteria for resuming treatment.

After study unblinding (see Section 3.1.5), no further OLT will be initiated and ongoing OLT will be discontinued after OLT Week 52. Subsequent access to obinutuzumab may occur through post-trial access (see Section 4.3.4).

Patients who discontinue OLT will enter SFU (see Section 3.1.4).

3.1.4 Study Follow-Up

Patients will be followed through Week 76 and for at least 12 months from the last dose of obinutuzumab or placebo:

- Patients who discontinue infusions prior to Week 76 will complete all visits through Week 76 according to the original schedule of activities before entering SFU.
- Patients who do not continue blinded infusions or enter open-label treatment based on the Week 76 assessment will enter SFU.
- Patients who discontinue all infusions (blinded and open-label) beyond Week 76 will enter SFU.

The first SFU visit will be scheduled approximately 6 months after the previous study visit (e.g., 6 months after Week 76). During SFU, patients will return for regular assessments every 6 months. Background immunosuppression, including MMF and corticosteroids, may be adjusted at the investigator's discretion. Obinutuzumab infusions will not be provided. Investigators and patients will not be unblinded to treatment assignment (except through emergency unblinding; see Section 4.2).

Those patients that have not reached B cell recovery, defined as peripheral CD19+ B-cell count at the lowest patient's pretreatment level or the lower limit of normal for the population under study, whichever is lowest, and who have not received a rescue therapy associated with reductions in peripheral B-cells (e.g., rituximab, cyclophosphamide, or use of obinutuzumab outside the study protocol) will continue to be followed every 6 months until any of the following occurs:

- Return of peripheral CD19+ B cells to the lowest pretreatment value or the lower limit of normal for this lupus population, whichever is lower
- Receipt of a therapy associated with reductions in peripheral B cells (e.g., rituximab or cyclophosphamide, or use of obinutuzumab outside the study protocol)
- Until end of study as outlined in Section 3.2

These represent the minimum required duration of follow-up for patients in the study. Investigators are encouraged to consider continuing SFU visits every 6 months until study unblinding occurs (see Section 3.1.5), at which point all patients who no longer require follow-up will complete the study.

After study unblinding has occurred (see Section 3.1.5), investigators may elect for patients to complete the study without completing the required 12 months of follow-up for the purpose of obtaining timely access to obinutuzumab infusions outside the study protocol (e.g., through the Sponsor's continued access provision, see Section 4.3.4).

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

3.1.5 Study Unblinding

The primary efficacy and safety analyses will be performed after data is available for all patients through the Week 76 assessments or early study discontinuation. After the primary analysis the Sponsor will be unblinded to treatment assignment. In order to collect additional controlled data beyond Week 76 for those patients who have an adequate response, unblinding of investigators and patients will not occur until data is available for all eligible patients through one year of blinded follow-up beyond Week 76 and the analysis of data through this point has been completed.

Following study unblinding, blinded infusions will be discontinued, no further OLT will be initiated, and ongoing OLT will be completed after the OLT Week 52 infusion. Subsequently, patients will be referred to the Sponsor's continued access provision for obinutuzumab and MMF access (see Section 4.3.4) or enter SFU (see Section 3.1.4).

3.1.6 Study Completion

Patients will complete the study when any of the following occurs:

- SFU requirements have been completed (see Section 3.1.4) and either:
  - No further SFU is desired, or
  - Study unblinding has occurred (see Section 3.1.5)
- Study unblinding has occurred and the investigator intends to treat the patient with obinutuzumab outside the study protocol (e.g., through the Sponsor's continued access provision) without completing SFU

3.1.7 Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will be used to monitor study data on an ongoing basis. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines the committee's roles and responsibilities. The iDMC will meet regularly (frequency adjustable as required) to evaluate unblinded study data, which will be prepared for the committee by an independent Data Coordinating Center (iDCC). The iDMC will provide recommendations to the Sponsor's Data Review Board (DRB) chair as described in the iDMC charter. On behalf of the Sponsor, the DRB chair will accept or reject the recommendations.

3.2 END OF STUDY, LENGTH OF STUDY, AND DURATION OF PARTICIPATION

The end of this study is defined as the date when the last patient, last visit (LPLV), occurs or the date at which SFU is received from the last patient up to a maximum of 18 months from the last obinutuzumab infusion (blinded and open-label). The end of the study is expected to occur approximately 5 years after the last patient is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 8 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Obinutuzumab Dose and Schedule

Lupus nephritis is a chronic condition that requires long-term immunosuppression. Phase III dose selection is based on a review of efficacy and safety-response relationships observed in the Phase II NOBILITY study. In this study, obinutuzumab 1000 mg was administered as an IV infusion on Weeks 0, 2, 24, and 26, combined with standard-of-care immunosuppression and demonstrated efficacy and acceptable safety in LN patients. In NOBILITY, as in LUNAR, achievement of sustained peripheral B-cell depletion was associated with increased achievement of CRR. Strong positive correlations were observed between exposure (assessed as cumulative area under the concentration-time curve [AUC]) and response to treatment. In addition, B-cell depletion appeared to last longer in patients with higher exposure. There were no clear relationships observed between exposure and safety. The NOBILITY regimen resulted in continued B-cell depletion through Week 52, at which point 80% of obinutuzumab patients were depleted to $\leq$0.441 cells/μL. Peripheral B-cell repletion had occurred for the majority of patients by the next measurement at Week 104; only 8% of obinutuzumab patients remained depleted at Week 104.

These results led to the hypothesis that obinutuzumab infusions beyond Week 26 may increase the degree and duration of clinical benefit by maintaining B-cell depletion. In the present study, obinutuzumab 1000 mg or placebo will be administered at Day 1 and Weeks 2, 24, 26, 50, and 52 before assessment of the primary endpoint at Week 76. To provide additional pharmacokinetic and pharmacodynamics data to support the dosing of obinutuzumab for use in chronic treatment, obinutuzumab Arm 1 will receive two obinutuzumab 1000 mg infusions at Month 12 (Weeks 50 and 52), and obinutuzumab Arm 2 will receive one obinutuzumab 1000 mg infusion at Month 12 (Week 52) and a placebo infusion at Week 50. Simulations based on a population PK model developed on data from NOBILITY suggest both regimens will result in maintenance of adequate trough obinutuzumab levels to maintain B-cell depletion at Week 76. As no difference in renal response is expected at Week 76, based on the number of obinutuzumab infusions at Month 12, the obinutuzumab treatment arms will

be combined for all primary and secondary comparisons between obinutuzumab and placebo. Descriptive comparisons only will be made between the obinutuzumab treatment arms.

As described in Section 3.1, dosing after Week 76 will be determined based on the investigator's assessment of adequacy of treatment response and need for intensification of therapy. This process will enable expanded access to obinutuzumab after Week 76 while maintaining study blinding and providing controlled, comparative data among patients with an adequate response who remain on blinded infusions.

Adequate Response

If the investigator assesses that 1) an adequate treatment response has been achieved, 2) there is no need to intensify therapy, and 3) there are no unmanageable treatment-emergent adverse events, it is appropriate to continue blinded infusions of obinutuzumab 1000 mg or placebo every 6 months.

Incomplete Response with Some Improvement

Patients who meet all of the following criteria, as assessed by the investigator, will be eligible for OLT:

- Inadequate treatment response
- Clinically meaningful improvement from baseline in renal parameters or prior clinically meaningful improvement from baseline followed by worsening
- Need for intensification of therapy
- No unmanageable treatment-emergent adverse events

During OLT, obinutuzumab 1000 mg will be administered on OLT Day 1 and OLT Weeks 2, 24, 26, and 52. Obinutuzumab 1000 mg will subsequently be administered every six months. Prior to initiation of OLT, documentation of these criteria will be submitted to the Medical Monitor for review. Investigators may discuss the appropriateness of OLT directly with the Medical Monitor if needed.

This open-label regimen is appropriate for eligible patients from all treatment groups without revealing the randomized treatment assignment:

For patients initially randomized to placebo, obinutuzumab induction represents an intensification of therapy with the potential for clinical benefit.

For patients initially randomized to obinutuzumab, eligibility criteria require that the patient has exhibited a clinically meaningful response to obinutuzumab and that there are no unmanageable treatment-emergent adverse events. Retreatment with obinutuzumab in these patients, regardless of the randomized obinutuzumab treatment regimen, is supported by published clinical data with rituximab and population PK modeling from NOBILITY as summarized below.

Retreatment after Incomplete Response or Secondary Nonresponse

In a recent description of 117 rituximab-treated patients with SLE, 34 (29%) with British Isles Lupus Assessment Group (BILAG) Grade A renal involvement, greater peripheral B-cell depletion was observed with successive cycles of rituximab treatment and the degree of B-cell depletion was a consistent predictor of clinical response (Yusof et al. 2017). 83% and 85% of those treated with rituximab who had incomplete response or secondary nonresponse, respectively, subsequently achieved a major clinical response upon rituximab retreatment. Among 5 patients switched to a humanized anti-CD20 monoclonal antibody (ocrelizumab or ofatumumab), achievement of complete peripheral B-cell depletion was associated with restoration of clinical response. In summary, these data suggest a rationale for retreatment with obinutuzumab to overcome loss of response or incomplete response via greater B-cell depletion in eligible patients.

Population Pharmacokinetic Modeling

A population PK model was developed using data from NOBILITY, in which the concentration time course of obinutuzumab in LN patients is accurately described by a linear two-compartment model with a time-varying clearance component which decreases with time and is considered likely related to CD20 target reduction and proteinuria improvement over time. The main covariates influencing PK were body weight, baseline serum albumin concentration, and baseline IgG. The population PK model was also used to explore relationships between obinutuzumab exposure and PD, safety, and efficacy endpoints. Strong positive correlations were observed between exposure (assessed as cumulative AUC) and response to treatment. In addition, B-cell depletion appeared to last longer in patients with higher exposure. There were no clear relationships observed between exposure and safety. Based on these data, administration of the induction regimen after Week 76 may result in a greater exposure than the initial regimen in the presence of improvements in serum IgG and/or serum albumin from baseline. This is expected to result in greater depletion of CD19+ B-cells from peripheral blood and tissue in patients with a clinically meaningful but incomplete response to treatment and may confer additional clinical benefit.

Other Response

For patients who fail to achieve a clinically meaningful response (primary nonresponse) to the randomized therapies, who discontinue blinded infusions, who receive rescue therapy, and/or who have unmanageable treatment-emergent adverse events with the blinded treatment regimen, standard-of-care therapies will be used in SFU at the investigator's discretion.

3.3.2 Rationale for Patient Population

The population to be enrolled in this protocol will be similar to that enrolled in NOBILITY: patients with active or active/chronic ISN/RPS Class III or IV proliferative LN on a recent renal biopsy (within 6 months of screening or during screening) and elevated proteinuria (UPCR $\geq$ 1 g/g). Class III or IV LN patients have a poor prognosis and require significant

immunosuppressive therapy. Patients with Class V membranous nephritis in addition to Class III or IV LN on renal biopsy will be eligible. Patients entering the protocol may have either relapsing or newly diagnosed disease.

3.3.3 Rationale for Control Group

The background regimen of MMF and corticosteroids represents the current standard of care therapy for LN. The provision of no background immunosuppression in a placebo-controlled study would represent inadequate therapy for a population at risk for irreversible 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 samples to assess exploratory biomarkers will be collected in this study to improve understanding of variability seen for clinical outcome to obinutuzumab treatment. Predictive biomarker samples will be collected prior to dosing in an effort to identify patients with B-cell driven pathogenesis who are most likely to respond to obinutuzumab. PD biomarker assessment will evaluate the effects of obinutuzumab on B-cells and other immune cells, 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.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 252 patients with ISN/RPS 2003 Class III or IV LN will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age 18–75 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Active or active/chronic ISN/RPS 2003 Class III or IV proliferative LN by renal biopsy performed in the 6 months prior to screening or during screening (see Appendix 2)

  One or more active glomerular lesions must be present.

  Class V disease may be present in addition to Class III or IV.

  The local biopsy report will be used to determine eligibility.

- SLE according to the 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) Classification Criteria, which are met by the presence of Class III or IV LN (above) and current or past positive antinuclear antibody (ANA)

  Positive ANA is defined by ANA at a titer of ≥1:80 on HEp-2 cells or an equivalent positive ANA test at least once.

- UPCR ≥1 g/g on a 24-hour collection at screening
- Receipt of at least one dose of pulse methylprednisolone IV (≥250 mg) or equivalent for treatment of the current episode of active LN during the 6 months prior to screening or during screening, or to be given on Day 1 prior to the first infusion

  A maximum of 3 g methylprednisolone IV or equivalent during the 4 weeks prior to screening or during screening is allowed.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use highly effective contraception, as defined below:

  Women must remain abstinent or use <u>two</u> reliable methods of contraception, including at least one method with a failure rate of <1% per year, during study treatment and for 18 months after the final dose of obinutuzumab or placebo and 6 weeks after the final dose of MMF.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation; male sterilization; established, proper use of hormonal contraceptives that inhibit ovulation; hormone-releasing intrauterine devices; and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
  If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive

method used by the female partner that together result in a failure rate of $<1\%$ per year during the treatment period and for 90 days after the final dose of MMF. Men must refrain from donating sperm during this same period.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

4.1.2 Exclusion Criteria

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

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 18 months after the final dose of obinutuzumab or placebo or within 6 weeks after the final dose of MMF
- Women of childbearing potential, including those who have had a tubal ligation, must have a negative urine pregnancy test at screening. Positive urine test results will be confirmed with a serum pregnancy test.
- Severe renal impairment, as defined by eGFR <30 mL/min/1.73 m^2 (as estimated using the CKD-EPI equation) or the need for dialysis or renal transplantation
- Sclerosis in $>50\%$ of glomeruli on renal biopsy
- Presence of rapidly progressive glomerulonephritis, defined by any of the following:
  - Crescent formation in $\geq 50\%$ of glomeruli assessed on renal biopsy
  - Sustained doubling of serum creatinine during the 2 months prior to screening
  - The investigator's opinion that the patient has rapidly progressive glomerulonephritis
- Receipt of any of the following excluded therapies:
  - Any anti-CD20 therapy such as rituximab, ocrelizumab, or ofatumumab less than 9 months prior to screening or during screening
  - If an anti-CD20 therapy has been received between 9 and 12 months prior to screening, the peripheral $CD19^+$ B-cell count must be ≥ 25 cells/μL
  - Cyclophosphamide, tacrolimus, ciclosporin, or voclosporin during the 2 months prior to screening or during screening
  - Any biologic therapy (other than anti-CD20) such as, but not limited to, belimumab, ustekinumab, anifrolumab, secukinumab, or atacicept during the 2 months prior to screening or during screening
  - Oral inhibitors of Janus-associated kinase (JAK), Bruton's tyrosine kinase (BTK), or tyrosine kinase 2 (TYK2), including baricitinib, tofacitinib, upadacitinib, filgotinib, ibrutinib, or fenebrutinib or any investigational agent during the 2 months prior to screening or during screening

  - Any live vaccine during the 28 days prior to screening or during screening
- Severe, active central nervous system SLE, including retinitis, poorly controlled seizure disorder, acute confusional state, myelitis, stroke, cerebellar ataxia, or dementia
- High risk for clinically significant bleeding or any condition requiring plasmapheresis, intravenous immunoglobulin, or acute blood product transfusions
- Significant or uncontrolled medical disease which, in the investigator's opinion, would preclude patient participation
- HIV infection
  - For patients with unknown HIV status, HIV testing will be performed locally at screening if required by local regulations.
- Tuberculosis (TB) infection
  - Testing for latent TB will be performed at screening if required by local regulations or in accordance with local clinical practice. Testing for latent TB may be performed centrally if local testing is not available.
  - Latent TB after completion of appropriate treatment is not exclusionary.
- Active infection of any kind, excluding fungal infection of the nail beds
- Any major episode of infection that also fulfills any of the following criteria:
  - Requires hospitalization during the 8 weeks prior to screening or during screening
  - Requires treatment with IV antibiotics or anti-infectives during the 8 weeks prior to screening or during screening
  - Requires treatment with oral antibiotics or anti-infectives during the 2 weeks prior to screening or during screening

    Antibiotics or anti-infectives given in the absence of a major episode of infection are not exclusionary.
- History of serious recurrent or chronic infection
- History of progressive multifocal leukoencephalopathy (PML)
- History of cancer, including solid tumors, hematological malignancies, and carcinoma in situ, within the past 5 years
  - Patients with non-melanomatous carcinomas of the skin that have been treated or excised and have resolved are eligible.
- Major surgery requiring hospitalization during the 4 weeks prior to screening or during screening
- Current alcohol or drug abuse or history of alcohol or drug abuse within 12 months prior to screening or during screening
- Intolerance or contraindication to study therapies, including any of the following:

- History of severe allergic or anaphylactic reactions to monoclonal antibodies or known hypersensitivity to any component of the obinutuzumab infusion
- Intolerance or contraindication to oral or IV corticosteroids
- Intolerance to MMF
- Lack of peripheral venous access

- Any of the following laboratory parameters:
  - AST or ALT $>2.5\times$ ULN
  - Amylase or lipase $>2\times$ ULN
  - Neutrophils $<1.5\times10^3/\mu L$
  - Positive hepatitis B surface antigen (HBsAg)

    Patients who are HBsAg negative and hepatitis B core antibody (HBcAb) positive with no detectable hepatitis B virus (HBV) DNA are eligible but will require monthly HBV DNA monitoring until 12 months after the last dose of obinutuzumab or placebo.
  - Positive hepatitis C serology

    Patients with positive hepatitis C antibody test result with no detectable hepatitis C virus (HCV) RNA at least 6 months after completion of antiviral therapy are eligible but will require monthly HCV RNA monitoring until 12 months after the last dose of obinutuzumab or placebo.
  - Hemoglobin <7 g/dL, unless caused by autoimmune hemolytic anemia resulting from SLE
  - Platelet count $<25{,}000/\mu L$
  - Positive serum human chorionic gonadotropin measured at screening

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

The investigator or the investigator's research staff will provide patient eligibility information through the interactive 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. Patients randomized to receive obinutuzumab will be further randomized to receive one of the two obinutuzumab dosing schedules (1000 mg IV on Day 1 and Weeks 2, 24, 26, 50 and 52; or 1000 mg IV on Day 1 and Weeks 2, 24, 26, and 52) in a 1:1 ratio. All patients will receive blinded infusions on Day 1 and Weeks 2, 24, 26, 50, and 52.

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:

- Region
  - United States and Canada
  - Latin America and the Caribbean
  - Other
- Race
  - Black
  - Other

These stratification factors were selected given expected differences in response by region and race. LN is clinically heterogeneous in presentation and factors such as availability and intensity of standard of care therapies; socioeconomic status; and ethnicity are known to affect a patient's response to treatment (Tesar et al 2011). In particular, black race is associated with more aggressive disease (Korbet et al 2007).

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 (IgM, IgA), or ADA results during the study, as listed below, until the primary efficacy and safety analyses through Week 76.

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 emergency 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 *(non-emergency unblinding), they* should contact the Medical Monitor directly. *If the Medical Monitor agrees to patient unblinding, the investigator will be able to break the treatment code by contacting the IxRS. The investigator should document and provide an explanation for any premature unblinding.*

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 study drug.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are obinutuzumab/placebo and MMF. Prednisone, premedications, and rescue medications are considered non-investigational medicinal products (NIMPs). Appendix 15 identifies all investigational, auxiliary, and non-investigational medicinal products for this study.

Patients may have been taking MMF prior to joining the study given the role of MMF in treatment of proliferative LN as recommended by ACR and EULAR/ERA-EDTA treatment guidelines (Hahn et al. 2012; Bertsias et al. 2012; Fanouriakis 2019). Within the study, MMF will be dispensed for the first time at day of randomization when it will be considered IMP. MMF used prior to Day 1 by the patient will not be considered IMP.

Obinutuzumab and Placebo

Obinutuzumab and placebo will be supplied by the Sponsor as sterile liquid in 50-mL glass vials. For information on the formulation and handling of obinutuzumab/placebo, see the Obinutuzumab Immunology Investigator's Brochure and pharmacy manual.

Mycophenolate Mofetil

MMF will be supplied or reimbursed by the Sponsor. For information on the formulation and handling of MMF, see the local prescribing information.

4.3.1 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Sections 3.1.2 and 3.1.3.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for treatment interruption or discontinuation, and for resumption, for patients who experience adverse events are provided in Section 5.1.3.

4.3.1.1 Obinutuzumab and Placebo

Obinutuzumab 1000 mg or placebo will be administered by IV infusion during blinded treatment at Day 1 and Weeks 2, 24, 26, 50, and 52 as described in Section 3.1.2. Subsequent blinded infusions will occur at Week 80 and every 6 months thereafter for

patients with an adequate response at Week 76. OLT will follow the initial obinutuzumab treatment schedule with infusions on OLT Day 1; at OLT Weeks 2, 24, 26, 52, and every 6 months thereafter (see Section 3.1.3).

Instructions for the administration of obinutuzumab or placebo infusions are provided in Appendix 6.

4.3.1.2 Mycophenolate Mofetil

All patients will receive MMF from the baseline visit (Day 1) onward. MMF will be titrated by Week 4 to a target dose of 2.0–2.5 g/day in divided doses. For patients newly initiating MMF, the recommended initial dosage is 1.5 g/day given in divided doses with titration by 500 mg/week to 2.0–2.5 g/day by Week 4.

If the investigator believes a patient requires MMF doses in excess of 2.5 g/day, the Medical Monitor should be contacted to discuss whether the target dose should be increased.

MMF should be maintained at the target dose through Week 80. Adjustments to MMF dosing will be permitted because of intolerance and adverse events. The dosage should not exceed 2.5 g/day unless discussed with the Medical Monitor. The guidelines for MMF dosing and recommended dose adjustments are provided in Appendix 7.

After Week 80, background immunosuppression may be adjusted at the discretion of the investigator. Investigators may continue MMF or switch to azathioprine (target dose: 2 mg/kg/day) as permitted by treatment guidelines. These therapies should be provided and monitored in a manner consistent with the ACR and/or EULAR/ERA-EDTA treatment guidelines (Hahn et al. 2012; Bertsias et al. 2012; Fanouriakis 2019), or local clinical practice.

MMF will be provided to the patient for home administration. To assess patient compliance with self-administration of MMF, patients will be required to record the date they took each dose in a medication diary; missed doses will also be recorded. Patients will be instructed to bring all unused study medication and their medication diaries at specified study visits for assessments of compliance.

4.3.2 Additional Medications

4.3.2.1 Corticosteroid Administration

All patients will receive IV and oral corticosteroids for the treatment of LN, consistent with ACR and EULAR/ERA-EDTA treatment guidelines (Hahn et al. 2012; Bertsias et al. 2012; Fanouriakis 2019). Every effort must be made to follow the corticosteroid regimen described below to permit the primary comparison of obinutuzumab and placebo.

Intravenous Corticosteroid Treatment

During the 6 months prior to screening, during screening, or on Day 1 (prior to the first infusion), all patients must have received at least one dose of pulse-dose methylprednisolone IV (250–1000 mg) or equivalent for the treatment of the current episode of active LN. Where possible, pulse corticosteroids should be completed prior to screening. The maximum permitted dose of pulse corticosteroids during the 4 weeks prior to screening or during screening is 3 g methylprednisolone IV or equivalent. If not given during the 6 months prior to screening or during screening, a single dose of pulse-dose methylprednisolone IV (250–1000 mg) will be given in place of pre-infusion methylprednisolone 80 mg IV on Day 1 only (see Section 4.3.2.2).

At blinded obinutuzumab or placebo infusions at Day 1 and Weeks 2, 24, 26, 50, and 52, methylprednisolone 80 mg IV will be given to prevent IRRs (see Section 4.3.2.2). Oral prednisone should not be administered on days when pre-infusion methylprednisolone is given.

Oral Prednisone Treatment

All patients will receive oral prednisone and follow a standardized tapering schedule through Week 80. In regions where prednisone or the specified dose of prednisone is not readily available, an approximately equivalent dose of an oral corticosteroid with a similar duration of action may be substituted (see Appendix 4).

During screening, prednisone may be administered up to 0.5 mg/kg/day (maximum 60 mg/day) if clinically indicated. Oral prednisone should not be administered on all days when pre-infusion methylprednisolone is given.

On Day 2, all patients will receive oral prednisone 0.5 mg/kg/day (maximum 60 mg/day) and remain at this dose until the Week 2 visit. Beginning on Day 15, prednisone will be tapered to achieve a target dose of 5 mg/day by Week 24 according to the schedule in Table 2. Prednisone will be maintained at 5 mg/day from Week 24 until Week 80.

Table 2 Prednisone Tapering Schedule through Week 80

	Prednisone Dose (mg/day) [a]			
Days 2–14	30	40	50	60
Week 2	25	30	40	50
Week 4	25	25	30	40
Week 6	20	20	20	30
Week 8	15	15	15	20
Week 10	10	10	10	10
Week 12	7.5	7.5	7.5	7.5
Weeks 24–80	5	5	5	5

[a] Oral prednisone is started at 0.5 mg/kg/day (maximum 60 mg/day). Starting doses should be rounded to the nearest 10 mg dose or the nearest dose that is feasible based on the locally available oral prednisone dose strengths. An approximately equivalent dose of an oral corticosteroid with a similar duration of action may be substituted.

Corticosteroid Dose Increases

Treatment with higher doses of prednisone is permitted if judged clinically necessary by the investigator for renal and extrarenal flares (see Appendix 5). Use of intravenous corticosteroids during the study is strongly discouraged unless gastrointestinal involvement temporarily precludes the use of oral corticosteroids.

Patients may receive higher doses of corticosteroids for emergent illness or surgery if clinically indicated; the corticosteroid use should be limited to the minimum duration and dose necessary before resuming the prednisone taper.

Use of pulse steroids or sustained, high-dose corticosteroids from Week 64 onward is considered corticosteroid rescue, will result in nonresponse for subsequent efficacy assessments, and should be avoided (see Section 4.4.4.1).

Corticosteroid Treatment after Week 80

After Week 80, the prednisone dose may be adjusted at the discretion of the investigator. Oral prednisone should not be administered on days when pre-infusion methylprednisolone is given.

4.3.2.2 Premedications

For blinded infusions at Day 1 and Weeks 2, 24, 26, 50, and 52, the following premedications will be administered. The administration of all premedications must be completed between 30 and 60 minutes prior to the obinutuzumab or placebo infusion:

- Methylprednisolone 80 mg IV and
- Acetaminophen (650–1000 mg) orally (PO) and
- Diphenhydramine 50 mg PO or IV (or equivalent dose of a similar agent)

For blinded infusions at Week 80 and beyond, premedication with methylprednisolone will only be given to those patients who experienced an IRR with the previous blinded infusion. Acetaminophen and diphenhydramine will be administered prior to all infusions.

For patients who did not receive the required pulse dose of IV corticosteroids during the 6 months prior to or during screening, a single pulse dose of methylprednisolone IV (recommended: 250 mg; permissible range 250–1000 mg) will be given instead of pre-infusion methylprednisolone 80 mg IV on Day 1 only.

During OLT, all patients will receive premedication with methylprednisolone 80 mg IV through the OLT Week 52 infusion; subsequently, pre-infusion methylprednisolone will only be given to patients who experienced an IRR with the previous obinutuzumab infusion. Acetaminophen and diphenhydramine will be administered prior to all infusions.

Instructions for the administration of premedications are provided in Appendix 6.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study will be provided or reimbursed by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied 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.

4.3.4 Continued Access to Obinutuzumab and MMF

The Sponsor will offer continued access to Roche IMP (obinutuzumab and MMF) 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 Roche IMP (obinutuzumab and MMF) after completing the study (see Section 3.1.6) if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Roche IMP 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 Roche IMP (obinutuzumab and MMF) after completing the study if any of the following conditions are met:

- The Roche IMP 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 IMP or data suggest that the IMP is not effective for LN
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for LN
- Provision of the Roche IMP 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 website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment 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. Under certain circumstances, the Medical Monitor may assess that medications used by a patient more than 7 days prior to screening may need to be captured on the Concomitant Medications eCRF (e.g., COVID-19 vaccinations and latent TB treatment must always be captured on the Concomitant Medications eCRF).

4.4.1 Recommended Therapy

4.4.1.1 Antihypertensive Therapy

Patients should receive either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin-receptor blocker (ARB) titrated to adequate blood pressure control as recommended by the KDIGO (Kidney Disease: Improving Global Outcomes) Blood Pressure Work Group for chronic kidney disease (Becker et al. 2012). Patients should be on either an ACE inhibitor or ARB for at least 10 days prior to randomization. Combination therapy with ACE inhibitor and ARB is not permitted.

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 KDIGO Blood Pressure Work Group (Becker et al. 2012). 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., non-dihydropyridine 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 3.

ACE inhibitor and ARB therapy exposure during the second and third trimesters is known to induce human fetal toxicity (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 contraindicated during the second and third trimester of pregnancy.

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

Other antihypertensive agents that affect proteinuria must not be used prior to Week 80 unless discussed with the Medical Monitor. These include non-dihydropyridine calcium antagonists, aldosterone antagonists, and direct renin antagonists.

Table 3 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.

4.4.1.2 Antimalarial Medications

Antimalarial medications have been shown to attenuate the relative risk of a clinical flare-up and severe exacerbation of disease (Canadian Hydroxychloroquine Study Group 1991) and should be provided as background medication as is consistent with treatment guidelines and local clinical practice.

As antimalarials can impact proteinuria, antimalarial therapy (hydroxychloroquine, chloroquine, or quinacrine) should be initiated prior to Day 1 and should be maintained at a constant dose through Week 80.

Table 4 lists the antimalarial medications and dose ranges to be used during the course of the study.

Table 4 Suggested Dose Ranges for Antimalarial Medications

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

4.4.1.3 Vitamins and Supplements

Patients who are not already taking vitamin D (600–800 IU/day) and calcium supplements (1000–1200 mg/day) should start taking these supplements during screening. Investigators should follow current guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis, for example those published by the ACR (Buckley et al. 2017).

4.4.2 Permitted Therapy

4.4.2.1 Other Concomitant Therapy

HMG-CoA-Reductase Inhibitors and Bisphosphonates

HMG-CoA-reductase inhibitors ("statins") and bisphosphonates are permitted but may not be newly 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 should be made to keep their dosage stable to prevent confounding of study results.

4.4.3 Cautionary Therapy

4.4.3.1 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 obinutuzumab or placebo. 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); hepatitis B and COVID-19 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®, tetanus) are not prohibited; however, vaccines received during peripheral B-cell depletion may be ineffective.

4.4.4 Rescue Therapy and Treatment Failure

4.4.4.1 Rescue Therapy

Disease flares may be managed with temporary increases in corticosteroid doses while continuing the study treatment regimen (see Appendix 5). In some cases of worsening or severely active disease, the investigator may conclude that the patient has failed the randomized treatment regimen and requires rescue therapy. The randomized treatment assignment will not be unblinded at the time of rescue therapy. Therapies that are considered rescue include the following:

- Cyclophosphamide
- Anti-CD20 antibodies, including rituximab, ocrelizumab, ofatumumab, and obinutuzumab (if given outside the study protocol)
- Calcineurin inhibitors including ciclosporin, tacrolimus, and voclosporin
- Other investigational, biologic, or targeted therapies used for the treatment of SLE or LN

Because these rescue therapies may affect subsequent efficacy assessments, patients who receive rescue will be treated as nonresponders for subsequent efficacy analyses.

Because the safety of obinutuzumab in combination with these rescue therapies has not been studied, patients who receive rescue will discontinue obinutuzumab or placebo infusions and will not be eligible for open-label treatment (see exception for corticosteroid-only rescue, Section 4.4.4.1.1 below). These patients will continue to be followed according to the study schedule of activities through Week 76 and for at least 12 months from the last dose of obinutuzumab or placebo (see Section 3.1.4).

4.4.4.1.1 Corticosteroid Rescue

Use of high doses of corticosteroids shortly before the primary endpoint at Week 76 may affect this assessment and should be avoided. Administration of any of the following from Week 64 onward will be considered rescue:

- Methylprednisolone $\geq$ 100 mg IV or equivalent
- Prednisone $\geq$ 20 mg/day or equivalent (mean dose) over any 2-week period

Patients who receive corticosteroid rescue will be treated as nonresponders. Patients who receive rescue with corticosteroids alone are not required to discontinue obinutuzumab or placebo infusions and may be eligible for OLT if all eligibility criteria are met (see Section 3.1.3).

4.4.4.2 Treatment Failure

Treatment failure is present if any of the following criteria are met:

- New ESRD or need for chronic dialysis or renal transplantation
- Clinically significant, sustained worsening in UPCR and/or eGFR from Week 24 onward that leads the investigator to conclude the patient has failed the randomized treatment regimen
- Receipt of rescue therapy, except for corticosteroid-only rescue

Patients with treatment failure must discontinue obinutuzumab or placebo infusions and will be nonresponders for all subsequent efficacy analyses. These patients will continue to be followed according to the study schedule of activities through Week 76 and for at least 12 months from the last dose of obinutuzumab or placebo (see Section 3.1.4).

4.4.5 Prohibited Concomitant Therapies through Week 80

Through Week 80, use of the following concomitant therapies is prohibited:

- Non-steroidal anti-inflammatory drugs (NSAIDs), aside from prophylactic aspirin (unless discussed with the Medical Monitor; see note below)
- Calcineurin inhibitors
- Other nephrotoxic drugs
- Other immunosuppressive agents not specifically allowed in the study
- Live or attenuated vaccines (see Section 4.4.2.1)

The use of NSAIDs, with the exception of aspirin when given for prophylaxis of cardiovascular, cerebrovascular, or thrombotic events, 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 as described above will not be allowed prior to Week 80 and must be discontinued during the screening period when patients become eligible for study participation and fulfill exclusion criteria.

4.4.6 Concomitant Therapies after Week 80

After Week 80, it is recommended that ACE inhibitor or ARB therapy, antimalarial therapy, vitamin D, and calcium supplement therapies are continued in accordance with treatment guidelines and local clinical practice. Antimalarial doses may be adjusted after Week 80.

If necessary, use of NSAIDs and antihypertensive agents that affect proteinuria such as non-dihydropyridine calcium antagonists, aldosterone antagonists, and direct renin antagonists is permitted after Week 80.

After Week 80, the following concomitant therapies will continue to be prohibited:

- Calcineurin inhibitors
- Other nephrotoxic drugs
- Live or attenuated vaccines (see Section 4.4.2.1)

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and laboratory test values are acceptable.

At applicable sites, certain study assessments may be performed by a mobile nursing (MN) professional at the patient's home or another suitable location (such as work) to improve access and convenience for patients participating in the study. Mobile nursing visits may be scheduled for visits without infusions or efficacy evaluations and at visits during which no planned treatment decision is scheduled. If used, the Sponsor will select a healthcare company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a patient and the patient gives written informed consent to participate in MN visits, the MN network will communicate with the patient and the patient's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening 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 enrollment. 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, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. Under certain circumstances, the Medical Monitor may assess that medications used by a patient more than 7 days prior to screening may need to be captured on the Concomitant Medications eCRF (e.g., COVID-19 vaccinations and latent TB treatment must always be captured on the Concomitant Medications eCRF). At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

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

Limited, symptom-directed physical examinations should be performed at specified post baseline visits and as clinically indicated. 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.

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. Before, during, and after infusions, vital signs may also be collected while patient is in a semi-supine position. The same arm for blood pressure measurements should be used consistently throughout the study, if possible, and the position in which the blood pressure was taken should be documented in the eCRF. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

4.5.5 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to one or several central laboratories for analysis (except where specified as a local laboratory test):

- Hematology: 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 (e.g., the direct Coombs' test), it will be performed locally.

- Blood chemistry: AST/SGOT, ALT/SGPT, alkaline phosphatase, amylase (at screening only), lipase (at screening only), total protein, albumin, cholesterol, total bilirubin, BUN, uric acid, creatinine, random glucose, potassium, sodium, chloride, calcium, phosphorus, lactic dehydrogenase, CPK, cystatin C, and triglycerides
- Urinalysis: dipstick for blood, nitrite, protein, and glucose and urine microscopy

  Preferably, UPCR analysis should be performed on a first morning void (FMV) (see Appendix 3).

- 24-hour urine collection: total protein, total creatinine, and creatinine clearance, and UPCR (see Appendix 3)
- Flow cytometry: B cell (CD19), T cell (CD3, 4, 8) and NK cells (CD16, CD56) via TBNK assay; B-cells and subsets (including CD19, CD27, CD38, IgD) via HSFC

  Flow cytometry results will remain blinded until the study is unblinded.

- Autoantibody profile (ANA, anti-dsDNA, anti-Sm, anti-RNP, anti-Ro, antiLa, antiC1q)
- Quantitative immunoglobulins: total, IgA, IgG, and IgM
- Complement: including C3, C4, and CH50
- Hemoglobin A_{1c}
- Antibody titers: Measurement of antibody titers to common antigens (mumps, Varicella, rubella, tetanus, and *Streptococcus pneumoniae*) will be performed according to the schedule of activities.

  This information will be used to assess the effect of obinutuzumab on specific humoral immunity to bacterial and viral antigens.

- Viral hepatitis: measurement of HBsAg, HBcAb, and HCV antibody

  Patients who are HBsAg negative and HBcAb positive will also be evaluated for HBV DNA.

  Patients who are HCV antibody positive will also be evaluated for HCV RNA.

- HIV serology

  For patients with unknown HIV status, HIV testing will be performed locally at screening if required by local regulations.

- Pregnancy test

  All women of childbearing potential (including those who have had a tubal ligation) will have a urine pregnancy test run locally at each visit. Positive urine test results will be confirmed with a serum pregnancy test at the central laboratory. The infusion must not be administered unless the serum pregnancy test is negative.
- Pharmacokinetics and immunogenicity: to be measured as outlined in the schedule of activities (see Appendix 1)
- Blood, serum, plasma, and urine samples for exploratory research on biomarkers and biomarker assay development
- Archival or newly collected kidney tissue samples for confirmation of renal histopathology and for exploratory research on biomarkers

Exploratory biomarker research may include, but will not be limited to, proteins and mRNA (including gene signatures) associated with B cells, B-cell subsets, and B-cell activity. Exploratory biomarkers in the urine may additionally include, but will not be limited to, proteins associated with kidney cell damage and immune cells. Research may involve extraction of RNA, analysis of proteins or protein fragments, other genomic variants, and genomic profiling through use of next-generation sequencing (NGS) of a comprehensive panel of genes. Genomic research will not be aimed at exploring inherited characteristics. NGS methods will not include whole genome sequencing (WGS) or whole exome sequencing (WES) of blood samples.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.10), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Serum samples collected for PK or immunogenicity analysis may be used for PK or immunogenicity assay development and validation or any other drug-related exploratory analyses; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood, plasma, serum, urine, and kidney tissue samples collected for biomarker research and biomarker assay development and validation will be destroyed no later than 5 years after the final Clinical Study Report has been completed

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.6 Electrocardiograms

Single ECG recordings will be obtained at screening and Week 76 visits, as outlined in the schedule of activities (see Appendix 1), and may be obtained at unscheduled timepoints as indicated.

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 recommended to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws). 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. Any ECG abnormalities should be reported in the eCRF.

4.5.7 Clinical Outcome Assessments

Patient-reported outcome (PRO) and clinician-reported outcome (ClinRO) instruments will be completed to assess the treatment benefit of obinutuzumab. In addition, PRO instruments will enable the capture of each patient's direct experience with obinutuzumab.

PRO data will be collected through use of the following instruments:

- FACIT-F Scale
- SF-36 v2 (Acute Version)
- EQ-5D-5L
- Subject Global Assessment (SGA)

ClinRO data will be collected through use of the following instruments:

- Physician's Global Assessment (PGA)
- SLEDAI-2K

4.5.7.1 Data Collection Methods for Clinical Outcome Assessments

PRO instruments will be self-administered at the clinic at specified timepoints during the study (see schedule of activities in Appendix 1). At the clinic, instruments will be administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment or procedures, unless otherwise specified.

PRO instruments, translated into the local language as appropriate, will be provided by the Sponsor

During clinic visits, PRO instruments should be administered as outlined below:

- Patients' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for patients to complete the instruments, estimated to be 30 minutes at each specified visit.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions, but may read questions verbatim upon request.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.
- Site staff should review all completed instruments and should ask the patient to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the patient to complete the item or confirm that the item was intentionally left blank.

ClinRO instruments will be completed at the clinic at specified timepoints during the study (see schedule of activities in Appendix 1). ClinRO instruments will be self-administered. The instruments will be provided by the Sponsor. Clinicians must complete the official version of each ClinRO instrument, as provided by the Sponsor. Instruments must not be copied from the protocol

4.5.7.2 Description of Clinical Outcome Assessment Instruments

SLEDAI-2K

The SLEDAI-2K is a validated instrument to assess SLE disease activity (see Appendix 9). It evaluates clinical symptoms and laboratory markers across nine organ systems and will be used to capture changes in lupus-related disease activity. SLE manifestations are assessed by the clinician if present within the last 30 days and added to determine the total SLEDAI-2K score, which ranges from 0 to 105. The SLEDAI-2K

score is to be taken at baseline, several subsequent scheduled visits throughout the study (see schedule of activities in Appendix 1), at an early study discontinuation visit, and at any unplanned visit related to a suspected extrarenal or lupus nephritis flare. It must be completed if new or worsening lupus symptoms or flares are observed at a scheduled visit when SLEDAI-2K is not part of the standard assessments.

FACIT-F Scale

The FACIT–F Scale is a patient-completed questionnaire consisting of 13 items that assess fatigue and has been validated in patients with SLE (Kosinski et al. 2013). Instrument scoring yields a range from 0 to 52, with higher scores representing better patient status (less fatigue). This questionnaire should be completed by the patient prior to any procedures being performed at the visit, if possible. The form should then be checked by site staff for completeness. A copy of the questionnaire can be found in Appendix 10.

SF-36 v2 (Acute Version)

The SF-36 v2 (Acute Version) is a 36-item generic health status measure that has been validated in patients with SLE (Stoll et al. 1997). It measures eight general health domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. These domains can also be summarized as physical and mental component scores. This questionnaire should be completed by the patient prior to any procedures being performed at the visit, if possible. The form should be checked for completeness by the site staff. A copy of the questionnaire can be found in Appendix 11.

EQ-5D-5L

The EQ-5D-5L is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analogue scale (VAS) that measures health state. The EQ-5D-5L is designed to capture the patient's current health status. Published weighting systems allow for creation of a single composite score of the patient's health status. The EQ-5D-5L takes approximately 3 minutes to complete. It will be used in this study for informing pharmacoeconomic evaluations. A copy of the questionnaire can be found in Appendix 12.

SGA

The Subject's Global Assessment of Disease Activity is the patient's overall assessment of his or her current disease activity. It is measured on a 100-mm horizontal VAS (see Appendix 13). The left-hand extreme of the line is described as "none" (symptom-free) and the right-hand extreme as "severe".

PGA

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 (see Appendix 14). The left-hand extreme of the line is described as "none" (symptom-free) and the right-hand extreme as "severe".

4.5.8 Diagnostic Renal Biopsy

For determination of study eligibility, the local biopsy report will be used. Where possible, the renal biopsy used for eligibility determination will be sent to a central specialist review laboratory before being returned to the study site. This central reading is not used to determine study eligibility. Micrographs may be transferred, if available, in lieu of tissue where transfer of tissue is not possible (e.g., not allowed per local regulation or insufficient sample).

4.5.9 Optional Renal Biopsy

Patients will be offered an optional renal biopsy following the Week 76 assessment and may undergo additional biopsies at any other time if deemed clinically appropriate by the investigator. This optional assessment may provide histologic evidence of disease activity or remission beyond the laboratory response measurements.

The Informed Consent Form will contain a separate section that addresses optional biopsies. A separate, specific signature will be required to document a patient's agreement to undergo optional biopsies. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

Samples may be used for exploratory biomarker research as described in Section 4.5.5. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. Refer to Section 4.5.5 for details on duration of sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.10 Optional Samples for Research Biosample Repository

4.5.10.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples 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.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- 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

4.5.10.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR 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 RBR sampling, this section of the protocol (Section 4.5.10) will not be applicable at that site.

4.5.10.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to obinutuzumab, diseases, or drug safety:

- Blood samples collected at the baseline (Day 1) visit and/or subsequent visits
- Leftover blood, serum, plasma, urine, and renal tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), including leftover tissue samples from medically indicated procedures (e.g., kidney biopsy) performed at the investigator's discretion during the course of the study

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via whole genome sequencing (WGS), whole exome sequencing (WES), or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger

dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.10.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples 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.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

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

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

4.5.10.5 Consent to Participate in the optional Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses optional participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent 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 RBR samples. 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 and (if applicable) the date(s) of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

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

4.5.10.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the Sample Informed Consent/Withdrawal eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.10.7 Monitoring and Oversight

RBR samples 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 samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. 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 RBR samples.

4.6 UNPLANNED VISITS

Unplanned visits may be performed if clinically indicated. Adverse events, concomitant medications, and vital signs must be assessed for each unplanned visit. Other procedures, tests, and assessments will be performed at the discretion of the investigator.

Patients who develop new or worsening lupus symptoms or for whom a flare is suspected should be seen at the investigational site, as soon as possible, regardless of

the dates of their scheduled study visits or the study period. SLEDAI-2K, urinalysis, including UPCR, chemistry panel, and additional procedures (see Appendix 1 schedule of activities) should be performed by the examining investigator (or their designee, as applicable) at all unplanned visits related to a suspected disease flare. For definition of renal and extrarenal flares, as well as, protocol guidance on corticosteroid dosing see Appendix 5. For reporting disease flares, see Section 5.3.5.10.

4.7 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.7.1 Study Treatment Discontinuation

Patients must permanently discontinue obinutuzumab or placebo infusions if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if study treatment is continued
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy
- Grade 4 IRR or recurrence of Grade 3 IRR upon re-challenge
- Grade 3 or 4 neutropenia that does not resolve to Grade $\leq$2 within 8 weeks
- Grade 3 or 4 thrombocytopenia (not due to SLE) 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 therapy as defined in Section 4.4.4.1

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced. Any patient who discontinues treatment should continue to undergo protocol-mandated visits.

4.7.2 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up

- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

In the case of patients who miss scheduled visits, site staff should make at least three attempts to contact the patient within a reasonable time period after the missed visit. The three attempts should be made with some reasonable time between and at different times of the day and by different methods if possible (e.g., telephone, email, and letter). Only after sufficient unsuccessful attempts at contact have been made may a patient be declared lost to follow-up.

4.7.3 Study 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
- 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.

4.7.4 Site Discontinuation

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 Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Obinutuzumab is currently approved in CLL and FL, and clinical development is ongoing in other malignancies such as NHL as well as in autoimmune diseases. The safety plan

for patients in this study is based on clinical experience with obinutuzumab in completed and ongoing studies. The anticipated important safety risks for obinutuzumab are outlined below. Please refer to the Obinutuzumab Immunology Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Obinutuzumab

5.1.1.1 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-CD20 monoclonal antibody), obinutuzumab patients appeared to have more IRRs compared to those receiving rituximab in patients being treated for hematologic malignancies.

In the NOBILITY study, at the Week 76 data cut, obinutuzumab was associated with increased non-serious infusion-related reactions (16% obinutuzumab vs. 10% placebo). All IRRs in obinutuzumab arm were non-serious. Of the 10 patients, the IRRs occurred at the first infusion in 8 patients; all IRRs resolved and none led to obinutuzumab discontinuation.

Details regarding management of IRRs can be found in Section 5.1.3.

5.1.1.2 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 greater 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.

In the NOBILITY study at the Week 76 data cut, a higher incidence of infections (serious and non-serious) was observed with obinutuzumab compared to placebo (70% vs. 64%). However, the placebo arm showed higher incidences of Grade ≥3 infection (21.0% vs. 4.8%) and serious infections (17.7% vs. 6.3%) compared to the obinutuzumab arm. Through Week 104, the incidence of infections (serious and non-serious) was 75% vs. 62% with obinutuzumab and placebo, respectively.

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 in hematologic malignancies.

No cases of hepatitis B reactivation were observed in the NOBILITY study as of the Week 104 data cut.

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.

5.1.1.3 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.

5.1.1.4 Neutropenia

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

In NOBILITY study as of the Week 76 data cut, three patients experienced four events of drug-related neutropenia in the obinutuzumab arm and two patients experienced three events in the placebo arm. Two of 4 events were grade 4 neutropenia in obinutuzumab arm. All events resolved. No events of drug-related neutropenia led to study or study drug discontinuation. No additional drug-related neutropenia events were seen through the NOBILITY study's Week 104 data cut.

5.1.1.5 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.

In the NOBILITY study, as of the Week 104 data cut, no events of drug related thrombocytopenia were reported.

5.1.1.6 Coagulation Abnormalities, Including Disseminated Intravascular Coagulation

Coagulation abnormalities, including disseminated intravascular coagulation (DIC), have been reported in patients receiving obinutuzumab for treatment of hematologic malignancies (FL and CLL). In the majority of cases, the events involved subclinical (asymptomatic) changes in platelets and laboratory coagulation parameters following the first infusion, with spontaneous resolution usually occurring by Day 8. In some cases, the events were associated with IRRs and/or tumor lysis syndrome. No specific baseline risk factors for DIC have been identified in patients treated with obinutuzumab.

In the NOBILITY study, as of the Week 104 data cutoff, no events of coagulation abnormalities including DIC were reported.

5.1.1.7 B-Cell Depletion and Recovery

B-cell depletion is defined as levels of peripheral CD19+ B cells below the TBNK assay limit of quantitation using conventional flow cytometry. B-cell recovery has taken place whenever peripheral B cells are no longer depleted and is defined as peripheral CD19+ count at the lowest patient's pretreatment level or the lower limit of normal for the population under study, whichever is lowest.

Obinutuzumab in Lupus Nephritis

In NOBILITY, obinutuzumab 1000 mg infusions at Day 1 and Weeks 2, 24, and 26 resulted in peripheral B-cell depletion of 94% of patients at Week 52. At the next measurement at Week 104, 16% of obinutuzumab patients were depleted to ≤ 5 cells/μL.

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 0.079×10^9 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.

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.

5.1.1.8 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.

In NOBILITY, the proportion of patients experiencing immunoglobulin depletion (defined as serum levels below 0.7 g/L, 5.65 g/L, and 0.4 g/L for IgA, IgG, and IgM, respectively) at Week 76 were as follows:

- IgA: 7.0% in the obinutuzumab arm vs. 2.0% in the placebo arm
- IgG: 10.5% in the obinutuzumab arm vs. 8.2% in the placebo arm
- IgM: 38.6% in the obinutuzumab arm vs. 10.2% in the placebo arm

5.1.1.9 Gastrointestinal Perforation

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.

In the NOBILITY study, as of the Week 76 data cut, 1 (1.6%) patient in the placebo arm and 2 patients (3.2%) in the obinutuzumab arm experienced GI perforation-related events. No additional GI perforation events were seen through the NOBILITY study's Week 104 data cut.

5.1.1.10 Worsening of Pre-Existing Cardiac Conditions

In patients with underlying cardiac disease, arrhythmias (such as atrial fibrillation and tachyarrhythmia), angina pectoris, acute coronary syndrome, myocardial infarction and heart failure have been reported during treatment with obinutuzumab for hematologic malignancies. These events may occur as part of an IRR and can be fatal. Therefore, patients with a history of cardiac disease should be monitored closely. In addition, these patients should be hydrated with caution in order to prevent a potential fluid overload.

In the NOBILITY study, at Week 104, 3 patients (5%) in the obinutuzumab arm and 3 patients (5%) in the placebo arm had experienced cardiac disorders. The patients in the obinutuzumab plus MMF arm experienced cardiac ventricular thrombosis (n = 2) and myocardial necrosis (in 1 patient, all Grade 3, non-serious, resolved with treatment), and Grade 1 tachycardia and Grade 1 bradycardia in 1 patient each.

5.1.2 Risks Associated with MMF

Please refer to prescribing information for MMF for a complete list of risks related to MMF.

5.1.3 Management of Patients Who Experience Adverse Events

5.1.3.1 Dose Modifications

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 to permanently discontinue obinutuzumab or placebo infusions, the patient should continue to be followed in the study for safety.

Please refer to Appendix 7 or prescribing information for MMF dose modification guidance.

5.1.3.2 Treatment Interruption

Obinutuzumab/placebo infusions may be slowed or withheld for patients who experience toxicity considered to be related to study drug (see Section 5.1.3.3).

In addition, prior to resuming either obinutuzumab/placebo study drug treatment:

- Any infection experienced at any time during the study must have fully resolved.
- ANC levels and platelet counts at the last blood sample analysis must not meet the study treatment discontinuation criteria (see Section 4.7.1).
- The patient must not have developed any of the following:
  - Active infection of any kind, excluding fungal infection of the nail beds
  - Significant or uncontrolled medical disease which, in the investigator's opinion, would preclude patient participation
- The patient must not be pregnant.

5.1.3.3 Management Guidelines

Guidelines for management of specific adverse events are outlined in Table 5. Additional guidelines are provided in the subsections below.

Table 5 Guidelines for Management of Specific Adverse Events

Event	Action to Be Taken
IRR	• Patients who have pre-existing cardiac or pulmonary conditions should be monitored carefully throughout the infusion and the post-infusion period. • Withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each obinutuzumab infusion and for the first hour after administration. • Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their anti-hypertensive medication. • 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. • Patients with known IgE-mediated hypersensitivity to obinutuzumab or any component of the obinutuzumab infusion must not be treated. • For additional guidance see Table 2 in Appendix 6 and Appendix 8.
Infections: General	• No patient will be enrolled with a major active infection or history of chronic or recurring infections (excluding fungal infection of skin and/or nail beds). • For all serious infectious adverse events, CBC with differential, quantitative immunoglobulins, and flow cytometry should be measured within 1 week of onset. • Patients who develop an active infection during the study will have obinutuzumab or placebo infusions withheld until the event has resolved. • MMF dose should be adjusted as per guidance in Appendix 7. • Patients who require vaccination should be vaccinated at least 28 days prior to receiving obinutuzumab or placebo. • Vaccination with live vaccine during study is contraindicated (see Section 4.4.3.1).

CSF = cerebrospinal fluid; GI = gastrointestinal; HBcAb = hepatitis B core antibody; HBV = hepatitis B virus; IRR = infusion-related reaction; IVIG = intravenous immunoglobulin; JC = John Cunningham; MMF = mycophenolate mofetil; MRI = magnetic resonance imaging; PML = progressive multifocal leukoencephalopathy.

Table 5 Guidelines for Management of Specific Adverse Events (cont.)

Event	Action to Be Taken
Infections: Hepatitis B	• Hepatitis B screening is required prior to initiation of obinutuzumab or placebo infusions. • Patients with active or chronic hepatitis B (surface Ag+) will be excluded from the study. • Patients who are core antibody positive (HBcAb+) with no detectable DNA will be allowed into the study but require monthly HBV DNA monitoring until 12 months after the last dose of obinutuzumab or placebo. Anti-viral therapy should be considered. • If HBV reactivation *(as defined in the most recent version of the obinutuzumab autoimmune Investigator's Brochure)* is observed: – Obinutuzumab or placebo infusions should be permanently discontinued (see Section 4.7.1). – Reduction or interruption of MMF should be considered, per local guidelines. – Antiviral therapy must be started as per EASL 2017 Clinical Practice guidelines or local guidelines. – Referral to a hepatologist is recommended. • Patients will be monitored regularly for transaminitis. If transaminitis is observed, patients will be promptly referred to a hepatologist for evaluation and treatment.
Suspected PML	• Stop obinutuzumab or placebo infusions and MMF. • Obtain neurological consult. • In consultation with a neurologist, we recommend obtaining an MRI and performing a lumbar puncture to assess for CSF JC viral DNA. • Notify monitors immediately.
Neutropenia	• Patients who experience neutropenia should be closely monitored with regular laboratory tests until resolution. • MMF dose should be adjusted as per guidance in Appendix 7. • If treatment is necessary, it should be administered in accordance with local guidelines and administration of granulocyte colony stimulating factors should be considered. • Any signs of concomitant infection should be treated as appropriate. • Grade 3 or 4 neutropenia that does not resolve to Grade ≤2 within 8 weeks is a treatment-discontinuation criterion. • 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.

CSF = cerebrospinal fluid; GI = gastrointestinal; HBcAb = hepatitis B core antibody; HBV = hepatitis B virus; IRR = infusion-related reaction; IVIG = intravenous immunoglobulin; JC = John Cunningham; MMF = mycophenolate mofetil; MRI = magnetic resonance imaging; PML = progressive multifocal leukoencephalopathy.

Table 5 Guidelines for Management of Specific Adverse Events (cont.)

Event	Action to Be Taken
Thrombocytopenia	• Patients should be closely monitored for thrombocytopenia, • 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. • Transfusion of blood products (i.e., platelet transfusion) according to institutional practice is at the discretion of the treating physician. • Thrombocytopenia that does not resolve to Grade ≤2 within 8 weeks is a treatment-discontinuation criterion. • Use of all concomitant therapies, which could possibly worsen thrombocytopenia related events such as platelet inhibitors and anticoagulants, should also be taken into consideration
Hypogammaglobulinemia	• Ig levels will be monitored throughout the study period. • IVIG should be considered for patients with recurrent/severe infections despite appropriate treatment, with concomitant hypogammaglobulinemia.
GI perforations	• Promptly evaluate patients presenting with new onset abdominal symptoms. • MMF dose should be adjusted as per guidance in Appendix 7.
Worsening of pre-existing cardiac conditions	• Closely monitor patients with underlying cardiac conditions • Caution to be taken when hydrating patients with underlying cardiac conditions to prevent a potential fluid overload

CSF = cerebrospinal fluid; GI = gastrointestinal; HBcAb = hepatitis B core antibody; HBV = hepatitis B virus; IRR = infusion-related reaction; IVIG = intravenous immunoglobulin; JC = John Cunningham; MMF = mycophenolate mofetil; 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 guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject 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) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- 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 NCI CTCAE; 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 are as follows:

- 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.

- *In addition to the above study level adverse events of special interest, adverse events of special interest for obinutuzumab include the following:* IRRs (see Section 5.1.1.1; Systemic IRRs only (local IRRs are not considered adverse events of special interest))
- Grade 3 or higher infections (see Section 5.1.1.2)
- Any hepatitis B reactivation and PML (see Section 5.1.1.2)
- Drug-related neutropenia (see Section 5.1.1.4)
- Drug-related thrombocytopenia (see Section 5.1.1.5)
- Gastrointestinal perforations (see Section 5.1.1.9)
- Worsening of pre-existing cardiac conditions (see Section 5.1.1.10)

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 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 will be reported until at least 12 months after the final dose of obinutuzumab or placebo. Additionally, for patients who require continued safety monitoring for continued B-cell depletion (see Section 3.1.4 for definition), adverse events will be reported until the earliest of the following occurs:

- Return of peripheral CD19+ B cells to the lowest pretreatment value or the lower limit of normal for this lupus population, whichever is lower
- Receipt of a therapy associated with reductions in peripheral B cells (e.g., rituximab or cyclophosphamide, or use of obinutuzumab outside the study protocol)
- Until end of study as defined in Section 3.2

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in 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 timepoints. 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 (v5.0) will be used for assessing adverse event severity. Table 6 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 6 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 [a]
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 [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] 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.

[c] 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 5.2.2.

[d] Grade 4 and 5 events not specifically listed in NCI CTCAE 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 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 Table 7):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of 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 7 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	An adverse event will be considered related, unless it fulfills the criteria specified below. 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 obinutuzumab or placebo infusions and are judged to be related to obinutuzumab or placebo infusions 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 obinutuzumab or placebo, 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

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 gastrointestinal 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 timepoints. 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. 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 timepoints 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

  Note: For oncology trials, certain abnormal values may not qualify as adverse events.

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 whether 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 ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$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 $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$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 LN.

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 solely to progression of SLE, "progression of systemic lupus erythematosus" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

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 need to be captured as efficacy assessment data through the SLEDAI-2K score instead. 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., inpatient 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 related to the study protocol (e.g., for obinutuzumab or placebo infusion or renal biopsy)
- 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

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 that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, 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). For obinutuzumab (or matching placebo), adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with obinutuzumab (or matching placebo), regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one

entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor. Sites are not expected to review the PRO data for adverse events.

5.3.5.14 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

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 trial. 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 (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information 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 Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all 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 paper Clinical Trial Adverse Event/Special Situations 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 at least until 12 months after the final dose of obinutuzumab/placebo or longer for patients who require a greater duration of follow-up (see Section 5.3.1). 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 paper Clinical Trial Adverse Event/Special Situations 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 serious adverse events that occur > 12 months after the final dose of obinutuzumab/placebo 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 through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 18 months after the final dose of obinutuzumab or placebo or within 6 weeks after the final dose of MMF. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), 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 90 days after the final dose of MMF. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), 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 obinutuzumab or placebo or MMF. When permitted by the site, the pregnant partner would need to sign 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 should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

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

A spontaneous 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).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity 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). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

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 trial-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.

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, email, 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 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (see Section 5.3.1 for definition), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special Situations 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 based on applicable legislation.

The Sponsor has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements for expedited safety reporting to regulatory authorities (which includes the use of applicable systems, such as EudraVigilance), IRBs, ECs, and investigators.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

Drug	Document
Obinutuzumab	Obinutuzumab Immunology Investigator's Brochure
MMF	Myfenax® European Summary of Product Characteristics

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

All efficacy outcomes will be analyzed using the efficacy-evaluable set that will include all randomized patients *regardless of whether they received study treatment*. 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 76 visit or discontinued from study. The primary efficacy and safety analyses will be performed on data for all patients through the Week 76 assessments or early study discontinuation. Further analyses will be performed once study unblinding occurs (see Section 3.1.5). Additionally, there will be a final safety analyses when all SFU is completed.

Safety assessments will be performed using safety-evaluable set defined as patients who have received any part of blinded infusion of obinutuzumab or placebo. 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

The primary efficacy endpoint of this study is the proportion of patients who achieve CRR. Based on the NOBILITY trial, it is estimated that approximately 30% of patients with proliferative LN who are receiving MMF will achieve CRR at Week 76 and that the addition of obinutuzumab to MMF will induce an overall CRR rate of 50% at Week 76. On the basis of these assumptions, a total of 252 patients randomized to obinutuzumab and placebo groups in a 1:1 ratio (126 patients in each of the obinutuzumab and placebo- treated-groups) stratified by region and race will yield approximately 90% power to compare the combined obinutuzumab treatment group with the placebo group at the two-sided $\alpha = 0.05$ significance level using a Cochrane-Mantel-Haenszel (CMH) test, assuming the same CRR proportions across the strata. Patients randomized to obinutuzumab-treated group will be further randomized to obinutuzumab Arm 1 and obinutuzumab Arm 2 in a 1:1 ratio stratified by region and race.

6.2 SUMMARIES OF CONDUCT OF STUDY

The numbers of patients who enroll, discontinue, or complete the study will be summarized by treatment group and study period. 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.

6.2.1 Summaries of Treatment Group Comparability

Demographic and baseline characteristics (including age, sex, serum creatinine, UPCR, weight, LN class, SLE and nephritis duration, race/ethnicity and region) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment group.

6.3 EFFICACY ANALYSES

The analysis set for the efficacy analyses will consist of all randomized patients *regardless of whether they received study treatment*, with patients grouped according to their assigned treatment. For all primary and secondary endpoints comparing the obinutuzumab and placebo groups, the obinutuzumab treatment groups will be combined.

6.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients who achieve CRR, evaluated at Week 76.

A patient will be considered a responder for CRR if the following conditions are met:

- UPCR <0.5 g/g
- eGFR $\geq 85\%$ of baseline, as calculated using the CKD-EPI equation
- No occurrence of *the following* intercurrent events:
  - Rescue therapy, treatment failure, *death or* early study withdrawal

The primary estimand attributes are as follows:

- Population: patients with active or active/chronic ISN/RPS 2003 Class III or IV proliferative lupus nephritis
- Primary endpoint (variable): CRR
- Treatments:
  - Experimental: obinutuzumab 1000 mg IV infusion at Day 1 and Weeks 2, 24, 26, and either Weeks 50 and 52 or Week 52 only
  - Control: placebo
- Intercurrent events: rescue therapy, treatment failure, *study treatment discontinuation, death* or early study withdrawal
- Handling of intercurrent events: *Rescue therapy, treatment failure, death and early study withdrawal are addressed in the endpoint definition and are handled under the* composite variable strategy. *Study treatment discontinuation will be handled using treatment policy strategy.*
- Summary measure: difference in proportion at Week 76

The proportions of patients achieving CRR across obinutuzumab (combined treatment groups) and placebo groups will be compared using a CMH test with region (United States and Canada vs. Latin America and the Caribbean vs. other) and race (Black vs. other) as stratification factors. The hypothesis test will be conducted at 5% level of significance (two-sided).

Serum creatinine (used to calculate eGFR) and 24-hour UPCR data obtained from the central laboratory will be used for efficacy analysis. eGFR will be calculated using the

CKD-EPI equation. If the baseline eGFR data is missing, then it will be imputed by the screening value. Details for handling missing eGFR and 24-hour UPCR postbaseline will be detailed in the Statistical Analysis Plan (SAP).

6.3.2 Secondary Efficacy Endpoints

6.3.2.1 Key Secondary Efficacy Endpoints

The estimand attributes for each key secondary endpoint and missing data handling strategies will be documented in the SAP. The key secondary efficacy endpoints are the following:

- Proportion of patients who achieve a proteinuric response at Week 76

  Proteinuric response is defined as achievement of all of the following:

  - UPCR <0.8 g/g
  - No occurrence of *the following* intercurrent events:
    - Rescue therapy, treatment failure, *death* or early study withdrawal
- Proportion of patients who achieve CRR with successful prednisone taper at Week 76, defined as achievement of CRR (as above) at Week 76 with the following:
  - No receipt of prednisone >7.5 mg/day (or equivalent) from Week 64 through Week 76
- Proportion of patients who achieve an ORR, defined as achievement of either CRR or PRR, evaluated at Week 50

  PRR is defined as achievement of all of the following:

  - $\geq 50\%$ reduction in UPCR from baseline
  - UPCR <1 (or <3 if the baseline UPCR was ≥ 3)
  - eGFR $\geq 85\%$ of baseline, as calculated using the CKD-EPI equation
  - No occurrence of *the following* intercurrent events:
    - Rescue therapy, treatment failure, *death* or early study withdrawal
- Proportion of patients who experience death or renal-related events through Week 76, defined as the proportion of patients with one or more of the following events:
  - Death
  - Treatment failure (see Section 4.4.4.2)
  - Worsening proteinuria, defined as a confirmed $\geq 50\%$ increase in UPCR to a value ≥ 3
  - Worsening eGFR, define as a confirmed $\geq 30\%$ decrease in eGFR to a value < 60
- Mean change in eGFR from baseline to Week 76
- *Change in FACIT-F scale from baseline to Week 76*

All the key secondary endpoints will be compared between obinutuzumab (combined treatment groups) and placebo groups. Proteinuric response, ORR and death or renal-related event will be analyzed similarly as the primary endpoint using a CMH test. Change from baseline in eGFR *and FACIT-F scale* will be analyzed by appropriate methods derived from estimand attributes and will be specified in the SAP.

To control for multiple comparisons, the primary and key secondary endpoints will be tested in a pre-specified order at a two-sided 0.05 significance level. The order of testing *and multiplicity control method* will be pre-specified in the SAP and finalized prior to database lock for the primary analysis.

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.

6.3.2.2 Supportive Secondary Efficacy Endpoints

The supportive secondary efficacy endpoints are listed below:

- Change in anti-dsDNA titer from baseline to Week 50
- Change in C3 from baseline to Week 50
- Change in SLEDAI-2K from baseline to Week 76
- Time to onset of CRR over the course of 76 weeks
- Proportion of patients who achieve CRR with serum creatinine criteria at Week 76

  CRR with serum creatinine criteria is defined as achievement of <u>all</u> of the following:
  - UPCR <0.5
  - Serum creatinine $\leq$ULN (as determined by the central laboratory)
  - Serum creatinine not increased from baseline by $>25\%$
  - No occurrence of *the following* intercurrent events:
    - *Rescue therapy, treatment failure, death or early study withdrawal*

All the supportive secondary efficacy endpoints will be compared between obinutuzumab (combined treatment groups) and placebo groups. CRR with serum creatinine criteria will be analyzed similarly as the primary endpoint using a CMH test. Change from baseline in anti-dsDNA, C3, SLEDAI-2K, and time to onset of CRR will be analyzed by appropriate methods derived from estimand attributes and will be specified in the SAP.

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

6.3.3 <u>Exploratory Efficacy Endpoints</u>

The exploratory efficacy endpoints are listed in Section 2.1.3.

Additionally, descriptive comparisons of the obinutuzumab treatment groups will be performed on the basis of the renal response endpoints.

Subgroup Analyses

Details of subgroup analyses will be specified in the SAP.

6.4 SAFETY ANALYSES

The safety-evaluable population is defined as patients who received any part of blinded infusion of obinutuzumab or placebo. Patients who were randomized to the study but who did not receive any part of blinded infusion of obinutuzumab or placebo will not be included in the safety population. Patients will be grouped according to the treatment that patients actually received rather than the treatment assigned. Patients who received any part of an infusion of obinutuzumab even if not assigned to obinutuzumab treatment group at randomization will be reported under the obinutuzumab treatment group. All safety analyses will be performed using the safety-evaluable population.

Safety will be assessed through summaries of exposure to study treatment, adverse events, adverse events in relation to ADAs, adverse events in relation to B-cell depletion and low Ig, changes in laboratory test results, and changes in vital signs and ECGs.

Study treatment exposure (such as treatment duration, total dose received, and dose modifications) will be summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature), and ECG abnormalities will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs will be summarized.

6.5 PHARMACOKINETIC ANALYSES

Serum obinutuzumab concentrations will be summarized (mean, minimum, maximum, SD and geometric mean) and reported in this study.

In addition, non-linear mixed effects modeling will be used to analyze the dose-concentration-time data of obinutuzumab. PK data will be used to refine the previously developed a pop PK model describing obinutuzumab PK following IV administration to LN patients including the effect of major covariates on the main parameters (e.g., clearance). Derivation of individual measures of exposure such as AUC and maximum observed concentration (C_{max}) will depend on the final model used for the analysis. The population PK analysis will be preceded by exploratory graphical evaluations of the data and will be used to assess the relationships between obinutuzumab exposure and efficacy, obinutuzumab exposure and safety. Relevant observed relationships between exposure and safety parameters and exposure and efficacy may be further characterized using different approaches such as logistic regression analyses. Additional PK and PD analyses may be conducted as appropriate. Results of the population PK and exposure-response/PD analyses may be reported separately.

6.6 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least one ADA assessment postdose. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment group. When determining post baseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post baseline samples is at least $\geq$4-fold greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all post baseline samples are negative, or if they are ADA positive at baseline but do not have any post baseline samples with a titer that is $\geq$4-fold greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints may be analyzed and reported via descriptive statistics.

6.7 BIOMARKER ANALYSES

The primary PD marker will be CD19+ B-cell counts. Exploratory PD markers from urine and blood samples will be summarized graphically and descriptively over time by cohort. 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 PD markers, obinutuzumab dosing and PK measures, and clinical response. The key exploratory analyses will be specified in the SAP.

6.8 HEALTH STATUS UTILITY ANALYSES

Change from baseline in EQ-5D-5L health utility index-based and VAS scores will be calculated at specified timepoints.

6.9 INTERIM ANALYSES

No interim analyses are planned.

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.

PRO and ClinRO data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

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 that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review 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, patient-reported outcomes, 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 trial.

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 and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-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 or paper PRO and ClinRO 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.

Roche will retain study data for 25 years after the final study results have been reported 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 (IND) 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 an Assent Form or Mobile 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.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. 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 (HIPAA) of 1996. 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

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.

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.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

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

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.5).

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 (see definition of end of study in Section 3.2).

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 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior

to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 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.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 150 sites globally will participate to enroll approximately 252 patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker, and PK analyses), as specified in Section 4.5.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An iDMC will be employed to monitor and evaluate patient safety throughout the study.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, 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 Information 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 trials 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 trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials 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 trials 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.

9.7 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 Activities

Table 1 Schedule of Activities through Week 76

	Screening [a]	Baseline	Treatment Visits										Unplanned Visit [b]	Early Study Discontinuation
Week	–4 to –1	0	2	4	12	24	26	36	50	52	64	76	NA	
Study Day	–28 to -1	1	14	28	84	168	182	252	350	364	448	532		
Informed consent	x													
IxRS [a]	x	x	x			x	x		x	x				x
Inclusion/exclusion criteria	x	x												
Demographic data	x													
Medical history and baseline conditions	x	x												
Patient-reported outcomes (SGA, FACIT-F, SF-36 v2, EQ-5D-5L) [c]		x				x			x			x	x [b]	x
Clinician-reported outcomes (PGA, SLEDAI-2K)		x				x			x			x	x [b]	x
Vital signs [d]	x	x	x	x		x	x		x	x		x	x	x
Weight	x	x				x [e]			x [e]			x		x
Height	x													
Complete physical examination [f]	x													
Limited physical examination [g]		x				x			x			x		x
Chest X-ray [h]	x													
ECG (12-lead)	x											x		
Hematology [i]	x	x	x	x	x	x	x	x	x	x	x	x	x [b]	x
Chemistry [j]	x	x	x	x	x	x	x	x	x	x	x	x	x [b]	x
Pregnancy test [k]	x	x	x	x	x	x	x	x	x	x	x	x		
Urinalysis [l]	x	x		x	x	x		x	x		x	x	x [b]	x
24-hour urine collection [m]	x	x				x			x			x		
HBsAg, HBcAb, HCV serology [n]	x	See Footnote n												
Quantitative serum Ig levels		x			x	x			x			x		x

Table 1 Schedule of Activities through Week 76 (cont.)

	Screening [a]	Baseline	Treatment Visits										Unplanned Visit [b]	Early Study Discontinuation
Week	–4 to –1	0	2	4	12	24	26	36	50	52	64	76	NA	
Study Day	–28 to -1	1	14	28	84	168	182	252	350	364	448	532		
Vaccination antibody titers [o]		x										x		x
Hemoglobin A_{1c}		x										x		x
Blood sample for flow cytometry [p]	x	x		x	x	x		x	x			x	x [b]	x
High-sensitivity flow cytometry [p]		x		x		x			x			x		
Complement (C3, C4, and CH50)	x	x		x	x	x			x			x	x [b]	x
Autoantibody profile [q]	x	x		x	x	x			x			x	x [b]	x
Antiphospholipid antibodies [r]		x										x		
Serum PK sample [s]		x	x	x	x	x	x	x	x	x	x	x	x [b]	x
Serum ADA sample [p]		x	x	x	x	x		x	x			x	x [b]	x
Plasma sample for biomarkers [p]		x				x			x			x		
Serum sample for biomarkers [p]		x		x	x	x			x			x	x [b]	
Urine sample for biomarkers [t]	x	x		x	x	x			x			x	x [b]	
Blood sample for DNA (optional) [u]		x												
Blood sample for RNA [p]		x		x	x	x			x			x		
Concomitant medications [v]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [w]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Blinded obinutuzumab or placebo administration [x]		x	x			x	x		x	x				
MMF dispensing [y]		x		x	x	x		x	x		x	x		
Prednisone taper [z]			x	x	x	x								
Renal biopsy [aa]	x													
Additional renal biopsy (optional) [bb]												x	x [b]	

Table 1 Schedule of Activities through Week 76 (cont.)

ADA=anti-drug antibody; CT=computed tomography; eCRF=electronic Case Report Form; EQ-5D-5L=EuroQol 5-Dimension, 5-Level Questionnaire; FACIT-F=Functional Assessment of Chronic Illness Therapy–Fatigue; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; IxRS=interactive Web response system; MMF=mycophenolate mofetil; PGA=Physician's Global Assessment; PK=pharmacokinetic; SF-36 v2=36-Item Short Form Survey, Version 2; SGA=Subject's Global Assessment; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; UPCR=urinary protein-to-creatinine ratio.

Notes: All assessments will be performed pre-infusion unless otherwise specified. Visits except for Day 1 should be performed within ±3 days of the scheduled visit. *However, an interval of 14 days should be kept between paired blinded obinutuzumab infusions (Days 1 & 14 (Week 2); Days 168 (Week 24) & 182 (Week 26); Days 350 (Week 50) & 364 (Week 52)), i.e. second of a course of two 6 monthly infusions interspersed by 2 weeks ('paired infusions').*

[a] At screening, IxRS will be contacted to obtain assignment of patient screening number. This will be the start of the 28 day screening window. At the discretion of the Medical Monitor, the maximum screening window of 28 days may be extended by up to 7 additional days to permit completion of subject eligibility assessment. At Day 1, IxRS will be contacted to obtain patient randomization number and drug assignment.

[b] Unplanned visits may be performed if clinically indicated. Adverse events, concomitant medications and vital signs must be assessed for each unplanned visit. Other procedures, tests, and assessments will be performed at the discretion of the investigator. However, in case of a change in lupus symptomatology or a suspected flare, the following tests should be performed for study purposes: urinalysis including UPCR, chemistry panel, hematology panel, flow cytometry, clinician reported outcomes (PGA and SLEDAI-2K), autoantibodies, complement C3 and C4 as well as samples for pharmacokinetics and ADA assessments. Any unplanned laboratory samples should also be sent to the central laboratory per instructions in the laboratory manual.

[c] Patient-reported outcomes will be performed prior to other assessments and procedures.

[d] Blood pressure and pulse rate (while patient is seated for 5 minutes), respiratory rate, and body temperature. Vital signs should be taken pre-infusion, then in seated or semi-supine position, 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.

[e] While the patient weight should be measured in order for the central laboratory to be able to calculate creatinine clearance, for these specific visits (Weeks 24 and 50), the weight does not need to be captured in the eCRF.

[f] A complete physical examination, performed at screening, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

[g] Limited, symptom-directed physical examinations should be performed at specified post baseline visits and as clinically indicated. 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.

Table 1 Schedule of Activities through Week 76 (cont.)

[h] If a chest X-ray or CT scan 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.

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

[j] 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, and phosphorus, CPK, cystatin C, and triglycerides. At screening, amylase and lipase will be also included.

[k] For women of childbearing potential, including those who have had a tubal ligation, a negative urine pregnancy test is required prior to all study drug infusions. If a urine test is positive, results will be confirmed with a serum pregnancy test prior to study drug administration. Study drug infusion must not be administered unless the serum pregnancy test result is negative.

[l] First morning urine sample is preferred. All urinalyses will be analyzed at the central laboratory and include microscopic examination, macroscopic urinalysis, and UPCR.

[m] To be analyzed for total protein, total creatinine, creatinine clearance, and UPCR.

[n] Patients who are HBsAg negative and HBcAb positive with no detectable HBV DNA are eligible but will require monthly HBV DNA monitoring until 12 months after the last dose of obinutuzumab or placebo. Patients who are HCV positive with no detectable HCV RNA at least 6 months after completion of antiviral therapy are eligible but will require monthly HCV RNA monitoring until 12 months after the last dose of obinutuzumab or placebo. For applicable sites, monthly HBV DNA monitoring and monthly HCV RNA monitoring can be done using mobile nursing.

[o] Antibody titers include mumps, rubella, Varicella, tetanus, and *Streptococcus pneumoniae*, as available per laboratory facility.

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

[q] Autoantibodies include, for example, anti-nuclear antibody, anti-dsDNA, Sm, Ro, La, and RNP.

[r] Antiphospholipid antibodies include anti-cardiolipin and anti-beta-2-glycoprotein antibodies.

[s] At infusion visits, obtain pre-infusion (recommended to be collected simultaneously with the earlier blood draw [prior to premedication] for the sake of patient comfort) and at the end of infusion (or within 30 minutes after the end of infusion). The timing of the PK sampling pre- and post-infusion should be precisely recorded. At non-infusion visits a single sample will be obtained.

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

[u] The DNA samples are optional and should only be obtained from patients who sign the separate Research Biosample Repository (RBR) Informed Consent Form. Preferably, samples will be obtained at baseline visit, but they may be obtained at subsequent study visits.

Table 1 Schedule of Activities through Week 76 (cont.)

[v] Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment 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. Under certain circumstances, the Medical Monitor may assess that medications used by a patient more than 7 days prior to screening may need to be captured on the Concomitant Medications eCRF (e.g., COVID-19 vaccinations and latent TB treatment must always be captured on the Concomitant Medications eCRF).

[w] On Day 1, adverse events will be recorded during infusion and post-infusion. For subsequent infusion visits, adverse events will be recorded pre-infusion, during infusion, and post-infusion. For all serious infectious adverse events reported, CBC with differential, quantitative immunoglobulins, and flow cytometry should be measured within 1 week of onset.

[x] At infusion visits, premedication with methylprednisolone 80 mg IV, acetaminophen 650−1000 mg PO (or equivalent dose of a similar agent), and diphenhydramine 50 mg PO or IV (or equivalent dose of a similar agent) will be given. The administration of these premedications should be completed between 30 and 60 minutes prior to the study drug infusion.

[y] For ex-U.S. sites, IxRS will be contacted in order to confirm MMF dispensing out of the central supply. For U.S. sites, MMF will be supplied locally and IxRS will not need to be contacted.

[z] Patients may initiate 0.5 mg/kg/day oral prednisone (maximum 60 mg/day) in screening or on Day 2. The prednisone taper will begin on Day 15. Oral prednisone should not be administered on all days when pre-infusion methylprednisolone is given.

[aa] Archival or newly collected kidney tissue samples for determination of patient eligibility. For determination of study eligibility, the local biopsy report will be used. Micrographs may be transferred, if available, in lieu of tissue when the transfer of tissue is not possible (e.g., not allowed per local regulation or insufficient sample).

[bb] All patients will be asked to undergo an optional repeat renal biopsy after completion of the treatment portion of the study (after Week 76). The optional repeat renal biopsy should occur during the 4 weeks after the Week 76 visit. 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 B-cell-related results.

Table 2 Schedule of Activities for Blinded Treatment after Week 76

	Blinded Treatment						Unplanned Visit [a]	Study Discontinuation
Year		2		3		4–6		
Week	80	106	132	158	184	Every 6 months thereafter [b]	NA	
Study Day	560	742	924	1106	1288			
IxRS [c]	x	x	x	x	x	x		x
Assessment of eligibility for continued blinded treatment [d]	x							
Patient-reported outcomes (SGA, FACIT-F, SF-36 v2, EQ-5D-5L) [e]		x	x	x	x	x	x [a]	x
Clinician-reported outcomes (PGA, SLEDAI-2K)		x	x	x	x	x	x [a]	x
Vital signs [f]	x	x	x	x	x	x	x	x
Weight	x [g]	x [g]	x [g]	x [g]	x [g]	x [g]		
Limited physical examination [h]		x		x				x
Hematology [i]	x	x	x	x	x	x	x [a]	x
Chemistry [j]	x	x	x	x	x	x	x [a]	x
Pregnancy test [k]	x	x	x	x	x	x		
Urinalysis [l]	x	x	x	x	x	x	x [a]	x
24-hour urine collection [m]	x [m]	x	x	x	x	x		
HBV DNA, HCV RNA [o]	See Footnote *o*							
Quantitative serum Ig levels		x	x	x	x	x		x
Vaccination antibody titers [p]				x		x		x
Hemoglobin A_{1c}		x		x				x
Blood sample for flow cytometry [q]	x	x	x	x	x	x	x [a]	x
High-sensitivity flow cytometry [q]		x	x	x	x	x		
Complement (C3, C4, and CH50)		x	x	x	x	x	x [a]	x
Autoantibody profile [r]		x	x	x	x	x	x [a]	x
Antiphospholipid antibodies [s]				x				x

Table 2 Schedule of Activities for Blinded Treatment after Week 76 (cont.)

	Blinded Treatment						Unplanned Visit [a]	Study Discontinuation
Year		2		3		4–6		
Week	80	106	132	158	184	Every 6 months thereafter [b]	NA	
Study Day	560	742	924	1106	1288			
Serum PK sample [t]	x	x	x	x	x	x	x [a]	x
Serum ADA sample [q]	x	x	x	x	x	x	x [a]	x
Plasma sample for biomarkers [q]	x	x		x				
Serum sample for biomarkers [q]	x	x		x			x [a]	
Urine sample for biomarkers [u]	x	x		x			x [a]	
Blood sample for RNA [q]	x	x		x				
Concomitant medications [v]	x	x	x	x	x	x	x	x
Adverse events [w]	x	x	x	x	x	x	x	x
Blinded obinutuzumab or placebo administration [x]	x	x	x	x	x	x		
MMF dispensing [y]	x	x	x	x	x	x		

ADA=anti-drug antibody; eCRF=electronic Case Report Form; EQ-5D-5L=EuroQol 5-Dimension, 5-Level Questionnaire; FACIT-F=Functional Assessment of Chronic Illness Therapy–Fatigue; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; IxRS=interactive Web response system; MMF=mycophenolate mofetil; PGA=Physician's Global Assessment; PK=pharmacokinetic; SF-36 v2=36-Item Short Form Survey, Version 2; SGA=Subject's Global Assessment; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; UPCR=urinary protein-to-creatinine ratio.

Notes: All assessments will be performed pre-infusion unless otherwise specified. Through Week 184, all visits should be performed within ±3 days of the scheduled visit. Subsequent visits should be performed within ±7 days of the scheduled visit.

Table 2 Schedule of Activities for Blinded Treatment after Week 76 (cont.)

[a] Unplanned visits may be performed if clinically indicated. Adverse events, concomitant medications and vital signs must be assessed for each unplanned visit. Other procedures, tests, and assessments will be performed at the discretion of the investigator. However, in case of a change in lupus symptomatology or a suspected flare, the following tests should be performed for study purposes: urinalysis including UPCR, chemistry panel, hematology panel, flow cytometry, clinician reported outcomes (PGA and SLEDAI-2K), autoantibodies, complement C3 and C4 as well as samples for pharmacokinetics and ADA assessments. Any unplanned laboratory samples should also be sent to the central laboratory per instructions in the laboratory manual.

[b] After Week 184 of blinded treatment, visits will occur approximately every 6 months as follows: at Weeks 210 and 236 for Year 4 of blinded treatment; at Weeks 262 and 288 for Year 5 of blinded treatment, and at Weeks 314 and 340 for Year 6 of blinded treatment.

[c] The first blinded infusion after Week 76 will occur at Week 80. At the Week 80 visit, IxRS will be contacted to confirm continued blinded treatment.

[d] Patients may continue blinded treatment if they meet adequate response criteria at Week 76. Refer to Section 3.1.2 for details.

[e] Patient-reported outcomes will be performed prior to other assessments and procedures.

[f] Blood pressure and pulse rate (while patient is seated for 5 minutes), respiratory rate, and body temperature. Vital signs should be taken pre-infusion, then in seated or semi-supine position, 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.

[g] While the patient weight should be measured in order for the central laboratory to be able to calculate creatinine clearance, for these specific visits (Weeks 80, 106, 132, 158, 184, and every 6 months thereafter), the weight does not need to be captured in the eCRF.

[h] Limited, symptom-directed physical examinations should be performed at specified post baseline visits and as clinically indicated. 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.

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

[j] 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, and phosphorus, CPK, cystatin C, and triglycerides.

[k] For women of childbearing potential, including those who have had a tubal ligation, a negative urine pregnancy test is required prior to all study drug infusions. If a urine test is positive, results will be confirmed with a serum pregnancy test prior to study drug administration. Study drug infusion must not be administered unless the serum pregnancy test result is negative.

[l] First morning urine sample is preferred. All urinalyses will be analyzed at the central laboratory and include microscopic examination, macroscopic urinalysis, and UPCR.

[m] To be analyzed for total protein, total creatinine, creatinine clearance, and UPCR.

Table 2 Schedule of Activities for Blinded Treatment after Week 76 (cont.)

[n] *Only required if the Week 76 24-hour urine collection was missing or could not be analyzed.*

[o] For patients who are HBsAg negative and HBcAb positive, perform monthly HBV DNA monitoring until 12 months after the last dose of obinutuzumab or placebo. Patients who are HCV positive with no detectable HCV RNA at least 6 months after completion of antiviral therapy are eligible but will require monthly HCV RNA monitoring until 12 months after the last dose of obinutuzumab or placebo. For applicable sites, monthly HBV DNA monitoring and monthly HCV RNA monitoring can be done using mobile nursing.

[p] Antibody titers include mumps, rubella, Varicella, tetanus, and *Streptococcus pneumoniae*, as available per laboratory facility.

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

[r] Autoantibodies include ANA, anti-dsDNA, Sm, Ro, La, and RNP.

[s] Antiphospholipid antibodies include anti-cardiolipin and anti-β-2-glycoprotein antibodies.

[t] At infusion visits, obtain pre-infusion (recommended to be collected simultaneously with the earlier blood draw [prior to premedication] for the sake of patient comfort) and at the end of infusion (or within 30 minutes after the end of infusion). The timing of the PK sampling pre- and post-infusion should be precisely recorded. At non-infusion visits a single sample will be obtained.

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

[v] Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment 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. Under certain circumstances, the Medical Monitor may assess that medications used by a patient more than 7 days prior to screening may need to be captured on the Concomitant Medications eCRF (e.g., COVID-19 vaccinations and latent TB treatment must always be captured on the Concomitant Medications eCRF).

[w] At Week 80, adverse events will be recorded during infusion and post-infusion. For subsequent infusion visits, adverse events will be recorded pre-infusion, during infusion, and post-infusion. For all serious infectious adverse events reported, CBC with differential, quantitative immunoglobulins, and flow cytometry should be measured within 1 week of onset.

[x] At infusion visits, premedication with acetaminophen 650−1000 mg PO and diphenhydramine 50 mg PO or IV (or equivalent dose of a similar agent) will be given. Premedication with methylprednisolone 80 mg IV should only be given if the patient experienced an infusion-related reaction with the previous infusion. The administration of all premedications should be completed between 30 and 60 minutes prior to the study drug infusion.

[y] For ex-U.S. sites, IxRS will be contacted in order to confirm MMF dispensing out of the central supply. For U.S. sites, MMF will be supplied locally and IxRS will not need to be contacted.

Table 3 Schedule of Activities for Open-Label Treatment

		Open-Label Treatment									Unplanned Visit [a]	Study Discontinuation
Week of Open-Label Treatment (OLT)	0 (Day 1)	2	4	12	24	26	36	52	76	Every 6 months thereafter [b]	NA	
IxRS	x [c]	x			x	x		x	x	x		x
Assessment of eligibility for open-label treatment [d]	x											
Patient-reported outcomes (SGA, FACIT-F, SF-36 v2, EQ-5D-5L) [e]	x				x			x	x	x	x [a]	x
Clinician-reported outcomes (PGA, SLEDAI-2K)	x				x			x	x	x	x [a]	x
Vital signs [f]	x	x	x		x	x		x	x	x	x	x
Weight	x [g]				x [g]			x [g]	x [g]	x [g]		
Limited physical examination [h]					x			x	x			x
ECG (12-lead)									x			
Hematology [i]	x	x	x	x	x	x	x	x	x	x	x [a]	x
Chemistry [j]	x	x	x	x	x	x	x	x	x	x	x [a]	x
Pregnancy test [k]	x	x	x	x	x	x	x	x	x	x		
Urinalysis [l]	x		x	x	x		x	x	x	x	x [a]	x
24-hour urine collection [m]	x [n]				x			x	x	x		
HBV DNA/HCV RNA [o]	See Footnote *o*											
Quantitative serum Ig levels	x			x	x			x	x	x		x

Table 3 Schedule of Activities for Open-Label Treatment (cont.)

		Open-Label Treatment									Unplanned Visit [a]	Study Discontinuation
Week of Open-Label Treatment (OLT)	0 (Day 1)	2	4	12	24	26	36	52	76	Every 6 months thereafter [b]	NA	
Vaccination antibody titers [p]	x								x			
Hemoglobin A_{1c}	x								x			x
Blood sample for flow cytometry [q]	x		x	x	x		x	x	x	x	x [a]	x
High-sensitivity flow cytometry [q]	x		x		x			x	x	x		
Complement (C3, C4 and CH50)	x		x	x	x			x	x	x	x [a]	x
Autoantibody profile [r]	x		x	x	x			x	x	x	x [a]	x
Antiphospholipid antibodies [s]	x								x			
Serum PK sample [t]	x	x	x	x	x	x	x	x	x	x	x [a]	x
Serum ADA sample [q]	x	x		x	x		x	x	x	x	x [a]	x
Plasma sample for biomarkers [q]	x				x			x	x			
Serum sample for biomarkers [q]	x		x	x	x			x	x		x [a]	
Urine sample for biomarkers [u]	x		x	x	x			x	x		x [a]	
Blood sample for RNA [q]	x		x	x	x			x	x			
Concomitant medications [v]	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [w]	x	x	x	x	x	x	x	x	x	x	x	x
Obinutuzumab administration [x]	x	x			x	x		x	x	x		
MMF dispensing [y]	x			x	x	x	x	x	x	x		

Table 3 Schedule of Activities for Open-Label Treatment (cont.)

ADA=anti-drug antibody; eCRF=electronic Case Report Form; EQ-5D-5L=EuroQol 5-Dimension, 5-Level Questionnaire; FACIT-F=Functional Assessment of Chronic Illness Therapy–Fatigue; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; IxRS=interactive Web response system; MMF=mycophenolate mofetil; PGA=Physician's Global Assessment; PK=pharmacokinetic; SF-36 v2=36-Item Short Form Survey, Version 2; SGA=Subject's Global Assessment; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; UPCR=urinary protein-to-creatinine ratio.

Notes: All assessments will be performed pre-infusion unless otherwise specified. Through OLT Week 76, all visits should be performed within ±3 days of the scheduled visit. *However, an interval of 14 days should be kept between paired blinded obinutuzumab infusions (OLT Days 1 & 14 (OLT Week 2); OLT Days 168 (OLT Week 24) & 182 (OLT Week 26); OLT Days 350 (OLT Week 50) & 364 (OLT Week 52), i.e. second of a course of two 6 monthly infusions interspersed by 2 weeks ('paired infusions').* Subsequent visits should be performed within ±7 days of the scheduled visit.

[a] Unplanned visits may be performed if clinically indicated. Adverse events, concomitant medications and vital signs must be assessed for each unplanned visit. Other procedures, tests, and assessments will be performed at the discretion of the investigator. However, in case of a change in lupus symptomatology or a suspected flare, the following tests should be performed for study purposes: urinalysis including UPCR, chemistry panel, hematology panel, flow cytometry, clinician reported outcomes (PGA and SLEDAI-2K), autoantibodies, complement C3 and C4 as well as samples for pharmacokinetics and ADA assessments. Any unplanned laboratory samples should also be sent to the central laboratory per instructions in the laboratory manual.

[b] After Week 76 of OLT, visits will occur approximately every 6 months as follows: at OLT Weeks 102 and 128 for Year 3 of OLT; at Weeks 154 and 180 for Year 4 of OLT, and at OLT Weeks 206 and 232 for Year 5 of OLT.

[c] For patients who enter OLT directly after Week 76, OLT will begin on Week 80 (OLT Day 1 [Week 0]). At this visit, IxRS will be contacted to confirm the start of OLT. OLT may only be initiated once 60 days have elapsed from the most recent obinutuzumab or placebo infusion.

[d] Patients may enter OLT if they meet inadequate response criteria at Week 76 or if there is loss of response during blinded treatment after Week 80. Refer to Section 3.1.3 for details.

[e] Patient-reported outcomes will be performed prior to other assessments and procedures.

[f] Blood pressure and pulse rate (while patient is seated for 5 minutes), respiratory rate, and body temperature. Vital signs should be taken pre-infusion, then in seated or semi-supine position, 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.

[g] While the patient weight should be measured in order for the central lab to have the information available, for these specific visits (Weeks 0 [Day 1], 24, 52, 76, and every 6 months thereafter) it does not need to be captured in the eCRF.

Table 3 Schedule of Activities for Open-Label Treatment (cont.)

[h] Limited, symptom-directed physical examinations should be performed at specified post baseline visits and as clinically indicated. 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.

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

[j] 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, and phosphorus, CPK, cystatin C, and triglycerides.

[k] For women of childbearing potential, including those who have had a tubal ligation, a negative urine pregnancy test is required prior to all study drug infusions. If a urine test is positive, results will be confirmed with a serum pregnancy test prior to study drug administration. Study drug infusion must not be administered unless the serum pregnancy test result is negative.

[l] First morning urine sample is preferred. All urinalyses will be analyzed at the central laboratory and include microscopic examination, macroscopic urinalysis, and UPCR.

[m] To be analyzed for total protein, total creatinine, creatinine clearance, and UPCR.

[n] *Only required if the Week 76 24-hour urine collection was missing or could not be analyzed.*

[o] For patients who are HBsAg negative and HBcAb positive, perform monthly HBV DNA monitoring until 12 months after the last dose of obinutuzumab or placebo. Patients who are HCV positive with no detectable HCV RNA at least 6 months after completion of antiviral therapy are eligible but will require monthly HCV RNA monitoring until 12 months after the last dose of obinutuzumab or placebo. For applicable sites, monthly HBV DNA monitoring and monthly HCV RNA monitoring can be done using mobile nursing.

[p] Antibody titers include mumps, rubella, Varicella, tetanus, and *Streptococcus pneumoniae*, as available per laboratory facility.

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

[r] Autoantibodies include ANA, anti-dsDNA, Sm, Ro, La, and RNP.

[s] Antiphospholipid antibodies include anti-cardiolipin and anti-beta-2-glycoprotein antibodies.

[t] At infusion visits, obtain pre-infusion (recommended to be collected simultaneously with the earlier blood draw [prior to premedication] for the sake of patient comfort) and at the end of infusion (or within 30 minutes after the end of infusion). The timing of the PK sampling pre- and post-infusion should be precisely recorded. At non-infusion visits a single sample will be obtained.

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

Table 3 Schedule of Activities for Open-Label Treatment (cont.)

[v] Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment 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. Under certain circumstances, the Medical Monitor may assess that medications used by a patient more than 7 days prior to screening may need to be captured on the Concomitant Medications eCRF (e.g., COVID-19 vaccinations and latent TB treatment must always be captured on the Concomitant Medications eCRF).

[w] At Week 80, adverse events will be recorded during infusion and post-infusion. For subsequent infusion visits, adverse events will be recorded pre-infusion, during infusion, and post-infusion. For all serious infectious adverse events reported, CBC with differential, quantitative immunoglobulins, and flow cytometry should be measured within 1 week of onset.

[x] At infusion visits, premedication with methylprednisolone 80 mg IV (see note below), acetaminophen 650−1000 mg PO and diphenhydramine 50 mg PO or IV (or equivalent dose of a similar agent) will be given. Beginning at the OLT Week 76 infusion, premedication with methylprednisolone 80 mg IV should only be given if the patient experienced an infusion-related reaction with the previous infusion. The administration of all premedications should be completed between 30 and 60 minutes prior to the study drug infusion.

[y] For ex-U.S. sites, IxRS will be contacted in order to confirm MMF dispensing out of the central supply. For U.S. sites, MMF will be supplied locally and IxRS will not need to be contacted.

Appendix 1: Schedule of Activities

Table 4 Schedule of Activities for the Study Follow-Up Period

	Study Follow-Up				Unplanned visit [a]	Study discontinuation
Week of Study Follow-Up (SFU)	0	26	52	Continued follow-up visits every 6 months (if needed) [b]	NA	
MMF dispensing [c]	x	x	x	x		
Vital signs [d]	x	x	x	x	x	x
Hematology [e]	x	x	x	x	x [a]	x
Chemistry [f]	x	x	x	x	x [a]	x
Pregnancy test [g]	x	x	x	x		
Urinalysis [h]	x	x	x	x	x [a]	x
HBV DNA/HCV RNA [i]	See Footnote i					
Quantitative serum Ig levels	x	x	x	x		x
Vaccination antibody titers [j]	x	x	x	x		
Blood sample for flow cytometry	x	x	x	x		
Concomitant medications [k]	x	x	x	x	x	x
Adverse events [l]	x	x	x	x	x	x

Table 4 Schedule of Activities for the Study Follow-Up Period (cont.)

eCRF = electronic Case Report Form; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; IxRS = interactive Web response system; MMF = mycophenolate mofetil; NA = not applicable; SFU = study follow-up; UPCR = urinary protein-to-creatinine ratio.

Notes: The first SFU visit will be scheduled approximately 6 months after the previous study visit (e.g., 6 months after Week 76). All visits should be performed within ±7 days of the scheduled visit.

[a] Unplanned visits may be performed if clinically indicated. Adverse events, concomitant medications and vital signs must be assessed for each unplanned visit. Other procedures, tests, and assessments will be performed at the discretion of the investigator. However, in case of a change in lupus symptomatology or a suspected flare, the following tests should be performed for study purposes: urinalysis including UPCR, chemistry panel, hematology panel, flow cytometry, clinician reported outcomes (PGA and SLEDAI-2K), autoantibodies, complement C3 and C4 as well as samples for pharmacokinetics and ADA assessments. Any unplanned laboratory samples should also be sent to the central laboratory per instructions in the laboratory manual.

[b] For patients with continued lack of peripheral B-cell recovery or who elect for additional SFU, visits will occur approximately every 6 months until study ends (Section 3.1.4).

[c] For Ex-U.S. sites, IxRS will be contacted in order to confirm MMF dispensing out of the central supply. For U.S. sites, MMF will be supplied locally and IxRS will not need to be contacted.

[d] Blood pressure and pulse rate (while patient is seated for 5 minutes), respiratory rate, and body temperature. Additional readings may be obtained at the discretion of the investigator.

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

[f] 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, and phosphorus, CPK, and triglycerides.

[g] For women of childbearing potential, including those who have had a tubal ligation, urine pregnancy tests will be performed at specified visits. If urine test is positive, results will be confirmed with a serum pregnancy test.

[h] First morning urine sample is preferred. All urinalyses will be analyzed at the central laboratory and include microscopic examination, macroscopic urinalysis, and UPCR.

[i] For patients who are HBsAg negative and HBcAb positive, perform monthly HBV DNA monitoring until 12 months after the last dose of obinutuzumab or placebo. Patients who are HCV positive with no detectable HCV RNA at least 6 months after completion of antiviral therapy are eligible but will require monthly HCV RNA monitoring until 12 months after the last dose of obinutuzumab or placebo.

[j] Antibody titers include mumps, rubella, Varicella, tetanus, and *Streptococcus pneumoniae*, as available per laboratory facility.

Table 4 Schedule of Activities for the Study Follow-Up Period (cont.)

[k] Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment 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. Under certain circumstances, the Medical Monitor may assess that medications used by a patient more than 7 days prior to screening may need to be captured on the Concomitant Medications eCRF (e.g., COVID-19 vaccinations and latent TB treatment must always be captured on the Concomitant Medications eCRF).

[l] For all serious infectious adverse events reported, CBC with differential, quantitative immunoglobulins, and flow cytometry should be measured within 1 week of onset.

Appendix 2
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
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 (≥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.

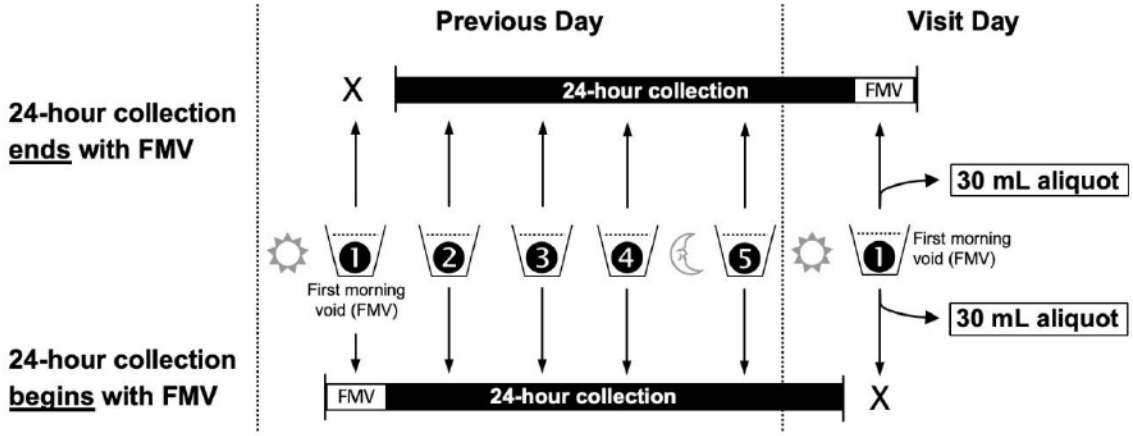
Appendix 3
Instructions for Collecting Urine Samples

At visits with 24-hour urine collections (e.g., Week 76), two urine samples are required:

- A 24-hour urine sample, that must include one first morning void (FMV), for measurement of the 24-hour urine protein to creatinine ratio (UPCR)
- A FMV sample in a separate container collected on the day of the visit, to provide a 30-mL aliquot for microscopic and macroscopic examination, spot UPCR measurement

There are two options for collecting these samples (see figure below):

- Option 1: 24-hour collection ends with FMV
  - The day prior to the visit, the patient should awaken from sleep, urinate, and discard (this FMV is not included in the 24-hour collection)
  - Over the next 24 hours, all urine is collected
  - The morning of the visit, the first void goes into a separate container and both samples (24 hour and FMV) are brought to the visit
  - At the site, a 30-mL aliquot will be taken from the FMV sample before the remaining FMV urine is added to the 24 hour collection
- Option 2: 24-hour collection begins with FMV
  - The day prior to the visit, the patient should awaken from sleep and begin the collection with the FMV
  - Over the next 24 hours, all urine is collected
  - The morning of the visit, the first void goes into a separate container and both samples (24 hour and FMV) are brought to the visit
  - At the site, a 30-mL aliquot will be taken from the FMV sample before the remaining FMV urine is discarded



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. A 30-mL aliquot is taken from this sample as well.

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.

THE 30-ML ALIQUOT URINE SAMPLE

30 mL is the recommended volume and 18 mL is the minimum necessary volume.

The sample should be split into two equal parts:

1. Central laboratory macroscopic and microscopic urinalysis
2. Spot UPCR

Additional urine microscopic and macroscopic analyses may be performed on a separate aliquot from the FMV urine sample using standard methods if desired. This is not required.

URINE SAMPLE FOR BIOMARKERS

The urine sample for biomarkers should be collected separately during the patient's visit (please see schedule of activities [Appendix 1] for visit days). Please refer to the laboratory manual for sample collection and processing instructions.

Appendix 4
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 5
Renal and Extrarenal Flares: Definitions and Corticosteroid Dosing

RENAL FLARE DEFINITION

Retreatment with higher doses of corticosteroids is permitted for treatment of renal flares if judged necessary by the investigator. Renal flare criteria require at least one of the following to be present (adapted from Rovin et al. 2005):

- Confirmed, clinically-significant increase in urinary protein-to-creatinine ratio (e.g., an increase of $\geq$50% to a value $>$3 that is confirmed with a repeated measurement)
- Confirmed, clinically significant decrease in estimated glomerular filtration rate (eGFR) (e.g., a decrease of $\geq$30% in eGFR from the previous assessment to a value $<$60 that is confirmed with a repeated measurement)

EXTRARENAL FLARE DEFINITION

Treatment with higher doses of corticosteroids is permitted for treatment of extrarenal flares if judged necessary by the investigator. An extrarenal flare is defined as a measurable increase in disease activity in one or more nonrenal organ systems involving new or worse clinical signs and symptoms that is clinically significant and prompts consideration of a change or increase in treatment (adapted from Ruperto et al. 2010).

Worsening of systemic lupus erythematosus (SLE) serologies (e.g., C3/C4, anti-dsDNA), or the presence of nonspecific symptoms for which an alternative etiology is likely (e.g., fever), do not, in isolation, constitute extrarenal flares.

SLE disease worsening and flares must be captured in the electronic data capture through the Systemic Lupus Erythematosus Disease Activity Index 2000 score electronic Case Report Form (see Section 4.5.7.2).

CORTICOSTEROID DOSING FOR RENAL AND EXTRARENAL FLARES

In the event of a renal or extrarenal flare, patients may receive prednisone up to 0.5 mg/kg (maximum 60 mg/day) for up to 2 weeks. Prednisone will then be tapered expeditiously to achieve $\leq$10 mg/day by 6 weeks after the initial corticosteroid increase (see Table 1). Subsequently, prednisone will be tapered back to the protocol-mandated dose (see Section 4.3.2.1). IV corticosteroids in equivalent doses may be used temporarily if gastrointestinal involvement temporarily precludes oral corticosteroid use.

Use of pulse steroids or sustained, high-dose oral corticosteroids from Week 64 onward is considered corticosteroid rescue, will result in nonresponse for subsequent efficacy assessments, and should be avoided (see Section 4.4.4.1.1).

Table 1 Prednisone Dosing for Renal and Extrarenal Flares

Weeks after Initial Corticosteroid Increase	Prednisone Dose [a] (mg/day)				
	20	30	40	50	60
2	15	25	30	40	50
3	15	20	25	30	40
4	≤10	15	20	20	30
5	≤10	≤10	15	15	20
6	≤10	≤10	≤10	≤10	≤10

[a] Oral prednisone may be given at up to 0.5 mg/kg/day (maximum 60 mg/day). Starting doses should be rounded to the closest 10 mg increment or the nearest increment that is feasible based on the locally available oral prednisone dose strengths. An approximately equivalent dose of an oral corticosteroid with a similar duration of action may be substituted if necessary.

Appendix 6
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.

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. Although obinutuzumab may be administered on an outpatient basis, patients may be observed in a hospital at the discretion of the investigator.

FIRST INFUSION (DAY 1)

Patients will receive premedication with methylprednisolone 80 mg IV, acetaminophen (650–1000 mg; or equivalent dose of a similar agent) by mouth (PO), and diphenhydramine 50 mg PO or IV (or equivalent dose of a similar agent) prior to the start of an infusion. The administration of all premedications must be completed between 30 and 60 minutes prior to the obinutuzumab or placebo infusion.

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

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 (mg/hr)	Infusion Rate (mL/hr)	Dose during time interval (mg)	Cumulative Dose (mg)
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 [a]	400	100	100	1000

[a] Should complete at 255 minutes (4 hours, 15 minutes) to complete total dose of 1000 mg.

In the event that the patient experiences an infusion-related reaction (IRR), refer to Table 2 below for infusion rate modification guidelines.

Table 2 Infusion Rate Modification Guidelines for Infusion-Related Reactions

Grade 4 (life-threatening)	Stop infusion and permanently discontinue therapy.
Grade 3 (severe)	Temporarily interrupt infusion and treat symptoms. Upon resolution of symptoms, restart infusion at no more than half the previous rate (the rate being used at the time that the IRR occurred). The infusion should be kept at the reduced rate for an additional 30 minutes. If patient does not experience any further IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose (see Table 1 'Schedule for First Infusions' or Table 3 'Schedule for Second and Subsequent Infusions'). If the patient experiences a second occurrence of a Grade 3 IRR, stop infusion and permanently discontinue therapy.
Grade 1–2 (mild and moderate)	Reduce infusion rate to half the infusion rate that was used at the time of the reaction (e.g., from 100 mg/hr to 50 mg/hr) and treat symptoms. Upon resolution of symptoms, the infusion should be kept at the reduced rate for an additional 30 minutes. If patient does not experience any IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose (see Table 1 'Schedule for First Infusions' or Table 3 'Schedule for Second and Subsequent Infusions').

IRR = infusion-related reaction.

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

Patients will receive premedication with methylprednisolone 80 mg IV (see note below), acetaminophen (650–1000 mg; or equivalent dose of a similar agent) PO, and diphenhydramine 50 mg PO or IV (or equivalent dose of a similar agent) prior to the start of an infusion. The administration of all premedications must be completed between 30 and 60 minutes prior to the obinutuzumab or placebo infusion.

During blinded treatment, premedication with methylprednisolone is required for the Day 1 and Week 2, 24, 26, 50, and 52 infusions only. Subsequently, methylprednisolone should only be given if the patient experienced an IRR with the prior infusion.

During open-label treatment (OLT), premedication with methylprednisolone is required regardless of prior IRR events through the OLT Week 52 infusion. Subsequently, methylprednisolone should only be given if the patient experienced an IRR with the prior infusion.

Patients who tolerated the first infusion of obinutuzumab or placebo may receive the second infusion as detailed in Table 3. Patients who experienced an IRR with the first infusion that is 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.

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 3 presents the schedule for the second and subsequent infusions.

In the event that the patient experiences an IRR, refer to Table 2 above for infusion rate modification guidelines.

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 3 Schedule for Second and Subsequent Infusions

Time (min)	Infusion Rate		Dose during time interval (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 [a]	400	100	100	1000

[a] Should complete at 195 minutes (3 hours, 15 minutes) to complete total dose of 1000 mg.

OPEN-LABEL INFUSIONS

For participants who receive OLT (see Section 3.1.3), the first open-label infusion will be administered according to the "first infusion" instructions presented in Table 1 above. Subsequent infusions will be administered according to the "second and subsequent infusions" instructions in Table 3.

Appendix 7
Guidelines for Mycophenolate Mofetil Dosing

TARGET DOSING

The target MMF dosage for the protocol is 2.0–2.5 g/day.

If investigators believe their patients require MMF doses in excess of 2.5 g/day, the Medical Monitor should be contacted to discuss whether the target dose should be increased.

INITIAL DOSING

Patients should be initiated on MMF at a dosage of 1.5 g/day in divided doses.

Patients already receiving MMF prior to study entry should be titrated to ≥1.5 g/day in divided doses by Day 1.

ESCALATION OF DOSE

The dosage of MMF should be increased, as tolerated, by 500 mg/week with the goal of reaching the target dose, in divided doses, by Week 4 at the latest.

ADJUSTMENTS TO MMF 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 2.5 g/day unless discussed with the Medical Monitor. The most common adverse effects requiring titration of MMF are gastrointestinal (GI) intolerance, neutropenia, and infectious complications (CellCept® U.S. Package Insert [USPI]). To maintain consistency in dose adjustments, recommended reductions are listed in Table 1.

If a patient develops GI toxicity due to MMF, 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 to a goal of 2 g/day 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. 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® (diphenoxylate and atropine), loperamide, or tincture of opium may be used to decrease diarrhea.

If a patient develops an 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 must be stopped immediately. The patient must return within 14–21 days for repeat measurement of ANC. If ANC is $>$1500, then MMF may be restarted at the "step 1" dose according to what the patient's previous MMF dose was. For example, if the patient's dosage of MMF was 2.5 g/day at the time of interruption of MMF, then MMF should be restarted at 2.0 g/day.

If a patient experiences an infectious complication, MMF should be stopped until the episode has resolved. MMF can then be reinstituted at the previous dose.

Regardless of dose reduction, every attempt must be made to bring the patient's dosage of MMF to $\geq$1.5 g/day.

Table 1 Protocol-Specified MMF Dose Reduction

MMF dosage (g/day)	Step 1 Reduction (g)	Step 2 Reduction (g)
2.5	2.0	1.5
2.0	1.5	1.0
1.5	1.0	0.5

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 8
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS

Anaphylaxis is highly likely when any one of the following three criteria are fulfilled (Sampson et al. 2006):

- Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least one of the following:
  - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
  - Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
- Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
  - Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
  - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
  - Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
  - Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
- Reduced BP after exposure to known allergen for that patient (minutes to several hours):
  - Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment infusion:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Antihistamines

- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
6. Continue to observe the patient and document observations.
7. Collect serum ADA sample for immunogenicity testing.

REFERENCES

Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391–7.

Appendix 9
SLE Disease Activity Index 2000 (SLEDAI-2K) (30 DAYS)

(Sample; Not to Be Used to Enter Subject Data)

Study No.: _____ Patient Name: _____ Visit Date: _____ _____ _____
d m yr

(Enter weight in SLEDAI-2K Score column if descriptor is present at the time of the visit or in the preceding 30 days)

SLEDAI 2K Weight	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 behavior. Exclude uremia 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 exudate 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 nonresponsive to narcotic analgesia.
8	_____	CVA	New onset of 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	$\geq$ 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion).
4	_____	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	_____	Urinary casts	Heme-granular or red blood cell casts.
4	_____	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	_____	Proteinuria	>0.5 gram/24 hours
4	_____	Pyuria	>5 white blood cells/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 electrocardiogram or echocardiogram confirmation.
2	_____	Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory
2	_____	Increased DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory.
1	_____	Fever	>38° C. Exclude infectious cause.
1	_____	Thrombocytopenia	<100,000 platelets / $x10^9$/L, exclude drug causes.
1	_____	Leukopenia	< 3,000 white blood cells / $x10^9$/L, exclude drug causes.
TOTAL SCORE	_____		

Appendix 10
FACIT-Fatigue

(Sample; Not to Be Used to Enter Subject Data)

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix 11
36-Item Short Form Survey (SF-36) (Version 2, Acute)

(Sample; Not to Be Used to Enter Subject Data)

SF-36 Acute Version

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. Compared to one week ago, how would you rate your health in general now?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
☐1	☐2	☐3	☐4	☐5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐1	☐2	☐3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐1	☐2	☐3
c. Lifting or carrying groceries	☐1	☐2	☐3
d. Climbing several flights of stairs	☐1	☐2	☐3
e. Climbing one flight of stairs	☐1	☐2	☐3
f. Bending, kneeling, or stooping	☐1	☐2	☐3
g. Walking more than a mile	☐1	☐2	☐3
h. Walking several hundred yards	☐1	☐2	☐3
i. Walking one hundred yards	☐1	☐2	☐3
j. Bathing or dressing yourself	☐1	☐2	☐3

4. **During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b. Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c. Were limited in the kind of work or other activities	☐1	☐2	☐3	☐4	☐5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

5. **During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b. Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c. Did work or other activities less carefully than usual	☐1	☐2	☐3	☐4	☐5

6. **During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

7. **How much bodily pain have you had during the past week?**

None	Very mild	Mild	Moderate	Severe	Very Severe
☐1	☐2	☐3	☐4	☐5	☐6

8. During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

9. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week:

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐1	☐2	☐3	☐4	☐5
b. Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
d. Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
e. Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
f. Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5
g. Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
h. Have you been happy?	☐1	☐2	☐3	☐4	☐5
i. Did you feel tired?	☐1	☐2	☐3	☐4	☐5

10. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐1	☐2	☐3	☐4	☐5
b. I am as healthy as anybody I know	☐1	☐2	☐3	☐4	☐5
c. I expect my health to get worse	☐1	☐2	☐3	☐4	☐5
d. My health is excellent	☐1	☐2	☐3	☐4	☐5

(SF-36v2 Acute, US Version 2.0)

THANK YOU FOR COMPLETING THESE QUESTIONS!

Appendix 12
EuroQol 5-Dimension Questionnaire, 5-Level Version (EQ-5D-5L)

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

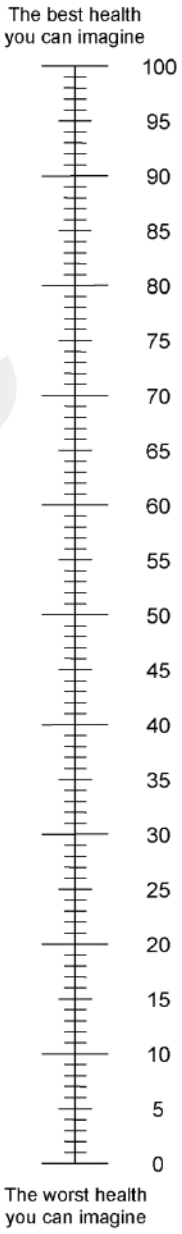
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 13
Subject's Global Assessment of Disease Activity

(Sample, Not to Be Used to Enter Subject Data)

SUBJECT'S GLOBAL ASSESSMENT (SCREENING)

Check if assessment was not done: ☐

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

Global Assessment of Disease Activity

On the line below, considering all the ways your Lupus affects you, where would you rate your Lupus symptoms over the last 10 days?

None _____ Severe

Site Measurement: °_____ mm

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

Appendix 14
Physician's Global Assessment of Disease Activity

(Sample. Not to Be Used to Enter Subject Data)

PHYSICIAN'S GLOBAL ASSESSMENT (SCREENING)

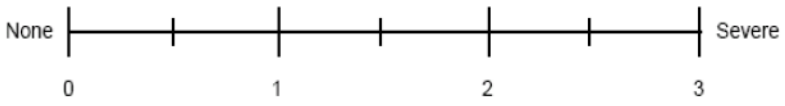
☐ Check if assessment was not done

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: ☐☐☐

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Appendix 15
Investigational Medicinal Product and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Table 1 Investigational, Authorized Auxiliary, and Unauthorized Auxiliary Medicinal Product Designations for European Economic Area

Product Name	IMP/NIMP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Gazyva® (RO5072759)	IMP (test product) [a]	Authorized	No [b]
Gazyva (RO5072759) placebo	IMP (placebo)	Authorized	No
Myfenax® (Mycophenolate mofetil)	IMP (test product)	Authorized	No
CellCept® (Mycophenolate mofetil) [c]	IMP (test product)	Authorized [c]	No
Corticosteroids	AxMP (Standard of Care)	Not applicable	Not applicable
Premedications to obinutuzumab	AxMP (Background treatment/Standard of Care)	Not applicable	Not applicable
Rescue Medication [d]	AxMP (other) [d]	Not applicable	Not applicable

AxMP = authorized auxiliary medicinal product.; EEA=European Economic Area; IMP=investigational medicinal product; LN =lupus nephritis; MMF=mycophenolate mofetil; PET=positron emission tomography; SLE=systemic lupus erythematosus.

[a] Gazyva (IMP) is a pharmaceutical form of an active substance being tested.

[b] Gazyva is approved for the treatment of chronic lymphocytic leukemia and follicular lymphoma.

[c] CellCept (Mycophenolate mofetil) may be used in the United States as MMF is sourced by sites.

[d] Rescue therapies including cyclophosphamide, anti-CD20 antibodies, calcineurin inhibitors, other investigational, biologic, or targeted therapies used for the treatment of SLE or LN.

Table 2 Investigational and Non-Investigational Medicinal Product Designations for United Kingdom

Product Name	IMP/NIMP Designation	Marketing Authorization Status in UK	Used within Marketing Authorization
Gazyva (RO5072759)	IMP (test product) [a]	Authorized	No [b]
Gazyva (RO5072759) placebo	IMP (placebo)	Authorized	No
Myfenax (Mycophenolate mofetil)	IMP (test product)	Authorized	No
CellCept (Mycophenolate mofetil) [c]	IMP (test product)	Authorized [c]	No
Corticosteroids	NIMP (Standard of Care)	Not applicable	Not applicable
Premedications to obinutuzumab	NIMP (Background treatment/Standard of Care)	Not applicable	Not applicable
Rescue Medication [d]	NIMP (other) [d]	Not applicable	Not applicable

EEA = European Economic Area; IMP = investigational medicinal product; LN = lupus nephritis; MMF = mycophenolate mofetil; NIMP = non-investigational medicinal product; PET = positron emission tomography; SLE = systemic lupus erythematosus.

[a] Gazyva (IMP) is a pharmaceutical form of an active substance being tested.

[b] Gazyva is approved for the treatment of chronic lymphocytic leukemia and follicular lymphoma.

[c] CellCept® (Mycophenolate mofetil) may be used in the United States as MMF is sourced by sites.

[d] Rescue therapies including cyclophosphamide, anti-CD20 antibodies, calcineurin inhibitors, other investigational, biologic, or targeted therapies used for the treatment of SLE or LN.

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