Official Title: A Phase III, International, Multicenter, Randomised Open Label Study to Evaluate the Efficacy and Safety of Obinutuzumab Versus MMF in Patients with Childhood Onset Idiopathic Nephrotic Syndrome

NCT Number: NCT05627557

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PROTOCOL

PROTOCOL TITLE:	**A PHASE III, INTERNATIONAL, MULTICENTER, RANDOMISED OPEN LABEL STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OBINUTUZUMAB VERSUS MMF IN PATIENTS WITH CHILDHOOD ONSET IDIOPATHIC NEPHROTIC SYNDROME**
PROTOCOL NUMBER:	WA43380
STUDY NAME	INShore
VERSION NUMBER:	3
TEST COMPOUND(S):	Obinutuzumab (RO5072759)
STUDY PHASE:	Phase III
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 157098 *EU CT Number: 2023-505140-19-00* EudraCT Number: 2022-000369-42 NCT Number: NCT05627557
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.

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PROTOCOL HISTORY

Protocol	
Version	**Date Final**
3	See electronic date stamp on final page of this document.
2	24 August 2022
1	1 April 2022

PROTOCOL AMENDMENT, VERSION 3

RATIONALE

Protocol WA43380 has been amended primarily [redacted] Substantive changes to the protocol, along with a rationale for each change, are summarized below.

- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol (front matter and 8.3.9).
- The synopsis has been simplified to align with CTR and other guidelines (Section 1.1).
- The requirement for systemic corticosteroid or other immunosuppressive treatments in the definition of relapse (in the primary endpoint) was removed to limit the potential for bias in this open-label study (Sections 1.1, 3 [Table 5] , 4.2.1, 6.1.4)
- The list of primary endpoint and key secondary endpoints have been simplified in Section 1.1 and 3 [Table 5] because detailed estimand attributes for each endpoint can be found in Section 9.
- Figure 1 has been revised to update the prednisone taper information.
- Study visits during which obinutuzumab will be infused and MMF will be dispensed are marked as corresponding IxRS visits in the Schedule of Activities (Section 1.3 Table 1)
- While the risk for obinutuzumab-associated coagulation abnormalities is low and hypothetical in patients without malignancy, the pediatric population with nephrotic disease is a vulnerable one. Therefore, additional local laboratory testing was added for exploratory purposes in an initial cohort of enrolled participants who are randomized to the obinutuzumab arm to assess platelet counts and coagulation profiles between Day 7 and the second infusion of obinutuzumab, scheduled to occur on Day 15 (Section 1.3 Table 1).
- For clarity, HIV and TB testing were added to the Schedule of Activities as laboratory tests to be performed at baseline only if required by local regulations (Section 1.3 Table 1).
- For clarity, additional text was added in the Schedule of Activities to instruct investigators to complete a relapse eCRF as close to the time of suspected relapse or during unscheduled visits occurring in the setting of a confirmed or suspected relapse (Section 1.3 Table 1).
- A list of laboratory tests to be prioritized in the setting of extenuating circumstances wherein obtaining all laboratory testing associated with a study visit is not possible was added (Section 1.3 Table 1).
- Patient diaries will prompt participants to contact study sites if either: 1) UA dipstick protein ≥3+ on any single day with edema (swelling); or 2) three consecutive days of UA dipstick protein ≥3+ occur. Text has been added to remind study sites to advise participants to contact the study site in the event of any of the above scenarios (Section 1.3 Table 1).

- [redacted]
- In the setting of obinutuzumab use for rescue therapy, the text was clarified to reflect that MMF must be discontinued (Section 4.1.2).
- A sub-section describing the role of the independent Data Monitoring Committee (iDMC) was added to the study design (Section 4.1.6).
- To align with the most recent diagnostic criteria for FRNS/SDNS, the recently published 2023 IPNA Clinical Practice Recommendations have been included in the inclusion criteria (Section 5.1) and a new Appendix 12.
- To align with the exclusion criteria from the Sponsor's other studies investigating obinutuzumab in adult and pediatric immunologic indications, , the exclusion criteria has been amended to revise the timeframe for excluding rituximab and similar biologic B cell-depleting therapies [redacted]. Washout period for any other biologic therapies (other than B cell depleting therapies) has also been clarified (Section 5.2).
- A comprehensive list of investigational medicinal products and auxiliary medicinal products has been added to align with CTR requirements (Section 6 and Appendix 13).
- Because the scale of the dispenser that was provided for administration of oral suspension MMF measures in 0.25 mL increments, instructions for liquid preparation of MMF were amended to round down to the nearest 0.25 mL (Section 6.1.2).
- Text regarding the treatment of relapse with [redacted] (Section 6.1.4).
- The text was amended to clarify that participants must discontinue study treatment with [redacted] (Section 6.1.4).
- For clarity and accuracy, the maximum MMF dose in the setting of study treatment [redacted] was amended to 2.0 g/day (Section 6.5).
- [redacted]
- Review of participants' COVID-19 immunization status prior to randomization was added (Section 6.8.2.1).
- Neutropenia thresholds for treatment discontinuation were clarified to include thresholds defined by both absolute neutrophil count thresholds as well as NCI CTCAE grading criteria (Section 7.1, Table A3-2).
- The discontinuation threshold for infusion related reactions (IRRs) was amended for children below 12 years of age such that treatment should be discontinued if an IRR is severe and deemed clinically serious (according to protocol-defined criteria for SAEs) or in the setting of escalation from moderate to severe IRR upon rechallenge. This revision was made to implement extra precautions in the treatment and clinical

management of the vulnerable population of children <12 years of age (Section 7.1, Table A10-3).

- The thrombocytopenia threshold for treatment discontinuation was amended in children below 12 years of age such that platelet counts remaining below 110,000 cells/µL for longer than 8 weeks in this population is a treatment discontinuation criterion. This revision was made to implement age-specific stopping criteria for children <12 years of age (Section 7.1, Table A3-2).
- A supplemental questionnaire for fatigue and physical functioning that will be administered at Week 52 was added (Section 8.1.2.2, A5-8, and A5-9).
- The text was amended to clarify that Adverse Events of Special Interest include systemic and not local IRRs (Section 8.3.8).
- The population attribute in the estimand attributes in Section 9 was revised to more accurately refer to patients with FRNS or SDNS.
- Treatment discontinuation due to adverse event, or any reason other than lack of efficacy, is now explicitly specified in the intercurrent events list for the primary and secondary endpoints. The methods to handle the intercurrent events are provided with the description of the estimands for the primary and key secondary endpoints, respectively. (Section 9).
- Pulse oximetry has been removed from the safety analysis since it will not be collected as a routine vital sign (Section 9.5.3).
- The secondary endpoint of Overall Relapse Free Survival was amended to include 'any systemic corticosteroid usage for > 14 days in a 30-day period, outside of the protocol defined steroid taper' to account of corticosteroid usage after the initial 8 weeks of protocol-defined steroid taper (Section 9.5.3).
- The intercurrent events strategy for the cumulative corticosteroid dose endpoint has been revised. All intercurrent events, except death, will be dealt with using the treatment policy strategy. A while-on-treatment strategy will be used for death (Section 9.5.3.2).
- The intercurrent events strategy for number of relapses has been revised. All intercurrent events, except death and rescue therapy, will be dealt with using the treatment policy strategy. A while-on-treatment strategy will be used for rescue therapy and death (Section 9.5.3.2).
- The intercurrent events strategy for clinical outcome assessments (fatigue/physical functioning/edema) has been revised. Treatment Policy Strategy will be used to deal with relapse, systemic corticosteroids usage for > 14 days in a 30 day period, and treatment discontinuation for any reason. While-on-Treatment Strategy will be used for the initiation of any rescue therapy for INS, as determined by the investigator's best medical judgement, other than systemic corticosteroids. Hypothetical Strategy will be used for death (Section 9.5.3.2).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with CTR requirements (A1-4 Data Protection).

- Due to certain local requirements and an alignment of Sponsor process, it has been clarified that summaries of clinical study results may be available in health authority databases for public access in addition to redacted Clinical Study Reports (A1-6 Dissemination of Clinical Study Data)
- IgE testing was removed as a central laboratory test, as this isotype is not required as part of the immunoglobulin testing (Table A6-1).

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

TABLE OF CONTENTS

PROTOCOL ACCEPTANCE FORM 12

1. PROTOCOL SUMMARY 13
   - 1.1 Synopsis 13
   - 1.2 Study Schema 19
   - 1.3 Schedule of Activities and Sample Collection Schedule 20

2. INTRODUCTION 33
   - 2.1 Study Rationale 33
   - 2.2 Background 33
   - 2.3 Benefit–Risk Assessment 35

3. OBJECTIVES AND ENDPOINTS 37

4. STUDY DESIGN 42
   - 4.1 Overall Design 42
   - 4.1.1 Screening 43
   - 4.1.1.1 Re-Testing: Laboratory Inclusion and Exclusion Criteria 43
   - 4.1.1.2 Re-Screening 43
   - 4.1.2 Study Treatment During the 52-Week Open-Label Treatment Period 44
   - 4.1.3 Post-Week 52 Extension Period 45
   - 4.1.4 Safety Follow-Up 46
   - 4.1.5 Study Completion 47
   - 4.1.6 *Independent Data Monitoring Committee* 47
   - 4.2 Rationale for Study Design 48
   - 4.2.1 Rationale for Primary Endpoint 48
   - 4.2.2 Rationale for Study Population 50
   - 4.2.3 Rationale for Control Group 51
   - 4.2.4 Rationale for Pharmacodynamic Biomarker Assessments 52
   - 4.2.5 Rationale for Open-label Study Design 52
   - 4.3 Justification for Dose and Schedule 52
   - 4.4 End of Study Definition 54
   - 4.5 Duration of Participation 54

5. STUDY POPULATION 55

5.1 Inclusion Criteria 55
5.2 Exclusion Criteria 56
5.3 Lifestyle Considerations 59
5.3.1 Meals and Dietary Restrictions 59
5.3.2 Caffeine, Alcohol, and Tobacco 59
5.3.3 Activity 59
5.3.4 Contraception Requirements 59
5.4 Screen Failures 59
6. STUDY TREATMENT(S) AND CONCOMITANT THERAPY 59
6.1 Study Treatments Administered 60
6.1.1 Obinutuzumab 63
6.1.2 Mycophenolate Mofetil 64
6.1.3 Oral Corticosteroid Treatment 65
6.1.4 Rescue Therapy 68
6.2 Preparation, Handling, Storage, and Accountability 70
6.3 Treatment Assignment 71
6.4 Study Treatment Compliance 71
6.5 Dose Modification 71
6.6 Continued Access to Study Treatment after the End of the Study 72
6.7 Treatment of Overdose 73
6.8 Concomitant Therapy 73
6.8.1 Other Permitted Therapy 74
6.8.2 Cautionary Therapy 74
6.8.2.1 Immunization during Peripheral B-Cell Depletion 74
6.8.2.2 Herbal Therapies 75
6.8.3 Prohibited Therapy 75
6.8.3.1 Prohibited Concomitant Therapies through Week 52 75
7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL 76
7.1 Discontinuation of Study Treatment 76
7.1.1 Liver Chemistry Stopping Criteria 77
7.2 Participant Discontinuation or Withdrawal from the Study 77

7.3 Participants Lost to Follow-Up 78
8. STUDY ASSESSMENTS AND PROCEDURES 78
8.1 Efficacy Assessments 80
8.1.1.1 Response Evaluation 80
8.1.2 Clinical Outcome Assessments 80
8.1.2.1 Pediatric Quality of Life Inventory—4.0 Generic Core Scale 80
8.1.2.2 Pediatric Quality of Life Inventory - Multidimensional Fatigue Scale 81
8.1.2.3 *Supplemental Questionnaire for Fatigue and Physical Functioning* 81
8.1.2.4 Cure Glomerulonephropathy Edema Scale 81
8.1.2.5 Subject Global Assessment of Disease Activity 81
8.1.2.6 Physician's Global Assessment of Disease Activity 82
8.2 Safety Assessments 82
8.2.1 Physical Examinations 82
8.2.2 Vital Signs 82
8.2.3 Electrocardiograms 82
8.2.4 Clinical Safety Laboratory Tests 83
8.2.5 Pregnancy Testing 84
8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting 84
8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information 84
8.3.2 Method of Detecting Adverse Events and Serious Adverse Events 85
8.3.3 Follow-Up of Adverse Events and Serious Adverse Events 85
8.3.4 Regulatory Reporting Requirements for Serious Adverse Events 85
8.3.5 Pregnancy 86
8.3.6 Cardiovascular and Death Events 87
8.3.7 Anticipated Events Not Qualifying for Expedited Reporting 87
8.3.8 Adverse Events of Special Interest 87
8.3.9 Medical Monitors and Emergency Medical Contacts 88
8.4 Pharmacokinetics 88

8.5 Pharmacodynamics 88
8.6 Genetics 88
8.7 Biomarker Assessments 89
[redacted] 89
8.9 Health Economics and Medical Resource Utilization 89
8.10 Additional Assessments and Procedures Requiring Separate Consent or Performed Only at Participating Sites 89
9. STATISTICAL CONSIDERATIONS 89
9.1 Statistical Hypotheses 90
9.2 Sample Size Determination 90
9.3 Analysis Sets 91
9.4 Statistical Analyses 91
9.5 Primary Endpoint 92
9.5.1 General Considerations 92
9.5.2 Primary Endpoint(s) 92
9.5.2.1 Definition of Primary Endpoint(s) 92
9.5.3 *Key/Confirmatory* Secondary Endpoints 94
9.5.3.1 *Time-to-Event Key Secondary Endpoints* 94
9.5.3.2 *Binary Key Secondary Endpoints* 95
9.5.3.3 *Continuous/Count Key Secondary Endpoints* 96
9.5.4 Exploratory Endpoints 98
9.5.4.1 Summaries of Conduct of Study 98
9.5.4.2 Summaries of Demographics and Baseline Characteristics 98
9.5.4.3 Pharmacokinetic Analyses 99
[redacted] 99
9.6 Interim Analysis/Analyses 100
9.7 China Subpopulation Analyses 100
10. REFERENCES 101

LIST OF TABLES

Table 1 Schedule of Activities for Initial Treatment Period (Screening to Week 52) 20
Table 2 Schedule of Activities for Extension Period (After Week 52 to Week 148 +) 27
Table 3 Schedule of Activities for Obinutuzumab Administration as Rescue Therapy or Post-Week 52 Repeat Treatment 30
Table 4 Schedule of Activities for the Safety Follow-Up Period 32
Table 5 Objectives and Corresponding Endpoints 38
Table 6 Study Treatment Description 61
Table 7 Oral Corticosteroid Tapering Guidelines 67
Table 8 Analysis Population Definition 91

LIST OF FIGURES

Figure 1 Study Schema 19

LIST OF APPENDICES

Appendix 1 Regulatory, Ethical, and Study Oversight Considerations 103
Appendix 2 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting 110
Appendix 3 Safety Plan: Management of Identified and Potential Risks 127
Appendix 4 Contraceptive and Barrier Guidance 140
Appendix 5 Clinical Outcome Assessment Instruments 143
Appendix 6 Clinical Safety Laboratory Tests 181
Appendix 7 Anaphylaxis Precautions 183
Appendix 8 Instructions for Collecting Urine Samples at Study Visits 185
Appendix 9 Instructions for Collecting Urine Samples at Home 186
Appendix 10 Obinutuzumab Dosing Schedule and Guidelines 187
Appendix 12 *International Clinical Practice Guidelines for the Diagnosis of Childhood-Onset FRNS or SDNS* 198
Appendix 13 *Investigational Medicinal Product and Non-Investigational Medicinal Product Designations (for Use in European Economic Area)* 199
Appendix 14 Abbreviations 200
Appendix 15 Protocol Amendment History 202

PROTOCOL ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE III, INTERNATIONAL, MULTICENTER, RANDOMISED OPEN LABEL STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OBINUTUZUMAB VERSUS MMF IN PATIENTS WITH CHILDHOOD ONSET IDIOPATHIC NEPHROTIC SYNDROME**
PROTOCOL NUMBER:	WA43380
STUDY NAME:	INShore
VERSION NUMBER:	3
TEST COMPOUND(S):	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 the Clinical Research Organization.

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**A PHASE III, INTERNATIONAL, MULTICENTER, RANDOMISED OPEN LABEL STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OBINUTUZUMAB VERSUS MMF IN PATIENTS WITH CHILDHOOD ONSET IDIOPATHIC NEPHROTIC SYNDROME**
REGULATORY AGENCY IDENTIFIER NUMBERS:	*IND Number: 157098* *EU CT Number: 2023-505140-19-00* *EudraCT Number: 2022-000369-42* *NCT Number: NCT05627557*

Study Rationale

The purpose of this open-label, randomized multicenter study is to assess the efficacy, safety, and pharmacokinetics (PK)/pharmacodynamics (PD) of obinutuzumab compared with mycophenolate mofetil (MMF) in children and young adults (aged ≥2–25 years) with frequently relapsing nephrotic syndrome (FRNS) or steroid-dependent nephrotic syndrome (SDNS).

Patients with childhood onset FRNS/SDNS are at risk of short-term and long-term steroid toxicity, severe infections, edema, thromboembolic events, and acute kidney injury during relapses. The reduction of these risks is dependent on the identification of effective therapy and the maintenance of clinical remission via sustained reduction in proteinuria. Current standard of care remains limited to a combination of systemic corticosteroids and immunosuppressive therapies, but most available regimens confer a complete renal response and remission in fewer than half of treated patients.

Objectives and Endpoints

This study will evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of obinutuzumab compared with MMF in participants aged between ≥2 and ≤25 years old with childhood onset FRNS or SDNS. Specific primary and secondary objectives and corresponding endpoints for the study are outlined below.

In this protocol, "study treatment" refers to the treatments assigned to participants as part of this study (i.e., obinutuzumab or MMF).

Primary Objective	Corresponding Endpoint
• To evaluate the efficacy of obinutuzumab compared with MMF	• Proportion of participants with sustained complete remission at 1 year, defined as first morning void UPCR ≤ 0.2 g/g at Week 52 without occurrence of a relapse or any *other* intercurrent *event as defined below.* *Participants experiencing any of the following intercurrent* events occurring after Week 8 *will be considered a non-responder*: 1. Relapse as defined by any of the following events [a]: a) First-morning void UPCR ≥ 2 g/g **or** b) Dipstick UA ≥ 3+ for 3 consecutive days (home-monitoring) and the most recent urine sample of the 3-day period determined to have UPCR > 0.2 g/g as measured by the central laboratory **or** c) Dipstick UA protein ≥ 3+ on any single day with edema and urine sample determined to have UPCR > 0.2 g/g as measured by the central laboratory 2. Any systemic corticosteroids usage for > 14 days in a 30 day period *Participants experiencing any of the following intercurrent events occurring after randomization will be considered a non-responder* [b,c]: 3. Initiation of any rescue therapy for INS, as determined by the investigator's best medical judgement, other than systemic corticosteroids 4. Treatment discontinuation due to lack of efficacy 5. Death
Secondary Objectives	**Corresponding Endpoints** [c]
• To evaluate the efficacy of obinutuzumab compared with MMF	• Overall *relapse-free survival (*RFS) • Probability of RFS at Week 52 • Cumulative corticosteroid dose • Number of relapses • Proportion of participants experiencing edema associated relapse *during the 52-week treatment period* [d] • Proportion of patients *with sustained complete remission at Week 76*

Secondary Objectives	Corresponding Endpoints [c]
• To evaluate changes in fatigue of participants treated with obinutuzumab compared with MMF	• *Mean* change in "General Fatigue" domain of PedsQL-Multidimensional Fatigue scale total score from baseline to Week 52
• To evaluate changes in the quality of life of participants treated with obinutuzumab compared with MMF	• *Mean* change in "Physical Functioning" domain of PedsQL Quality- of Life Inventory from baseline to Week 52
• To evaluate edema over time	• *Mean* change in CureGN Edema Scale from baseline to Week 52
• To evaluate the safety of obinutuzumab compared with MMF	• Incidence, nature, and severity of adverse events, with severity determined according to AE intensity (mild, moderate, severe, life-threatening) and NCI CTCAE grading if applicable from baseline to Week 52 • Incidence of laboratory or vital sign abnormalities from baseline to Week 52
• To characterize the obinutuzumab PK profile	• Serum concentrations of obinutuzumab at specified timepoints
• To characterize obinutuzumab-induced PD changes	• Proportion of participants achieving B-cell depletion (HSFC) at specified timepoints • Total peripheral B cell and B cell subsets (e.g., memory B cells) counts and change from baseline at specified timepoints

ADA=anti-drug antibodies; CureGN=Cure Glomerulonephropathy; eCRF=electronic Case Report Form; eGFR=estimated glomerular filtration rate; HSFC=highly sensitive flow cytometry; INS=idiopathic nephrotic syndrome; MMF=mycophenolate mofetil; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PD=pharmacodynamics; PedsQL=Pediatric Quality of Life Inventory; PGA=Physician's Global Assessment of Disease Activity; PK=pharmacokinetic; RFS=relapse-free survival; UA=urinalysis; UPCR =urinary protein-to-creatinine ratio; SGA=Subject Global Assessment of Disease Activity

[a] *The definition of relapse is the same throughout the study period. The definition of intercurrent event requires the relapse to have occurred after Week 8.*

[b] *The full list of intercurrent events (including those not treated as non-responders) are described in Section 9.5.2.1 .*

[c] *Details regarding the specification and handling of intercurrent events are included in Section 9.5.3 .*

[d] Edema-associated relapse definition is the same as the definition of relapse for the primary endpoint except that the edema-associated relapse definition additionally requires that patient edema is present and documented in the eCRF at the time of the relapse event.

OVERALL DESIGN *AND STUDY POPULATION*

This Phase III, randomized, open-label, multicenter, active comparator study *will* evaluate the efficacy, safety, and PK/PD of obinutuzumab versus MMF in maintaining remission in participants with childhood-onset FRNS or SDNS who have achieved complete remission upon study entry and are considered to be at high risk of relapse.

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

Phase:	*Phase III*	***Population Type:***	*Pediatric and adult patients*
Control Method:	*Active comparator*	***Population Diagnosis or Condition:***	*Childhood-onset FRNS or SDNS in complete remission*
Interventional Model:	*Parallel group*	***Population Age:***	*≥ 2–25 years old*
Test Compound[s]:	*Obinutuzumab*	***Site Distribution:***	*Multi-site and multi-region*
Active Comparator:	*MMF*	***Study Intervention Assignment Method:***	*Randomization*
Number of Arms:	*2*	***Number of Participants to Be Enrolled:***	*Approximately 80*

Study Treatment

The investigational medicinal products (IMP) for this study are obinutuzumab and MMF. Locally sourced prednisone, pre-medications used prior to infusions of obinutuzumab and standard-of-care rescue medications or other treatments or procedures initiated for INS per investigator discretion, are considered non-investigational medicinal products. Participants will be randomized in a 1:1 ratio to one of two open-label treatment groups: obinutuzumab (Group A) or MMF (Group B).

Randomized Group A: If participants are receiving MMF during screening, this must be discontinued by Day 1 randomization. Participants randomized to Group A will receive obinutuzumab 1000 mg (or 20 mg/kg for participants < 45 kg) to be administered by IV infusion on Days 1, 15, 168 (Week 24), and 182 (Week 26). See Appendix 10 for complete details on obinutuzumab and MMF administration.

The dose of obinutuzumab will be based on the participant's baseline weight (measured ≤ 14 days prior to initiation of study treatment) and will remain the same throughout the study unless the participant's weight changes by > 10% relative to the weight recorded at the time of the previous dose calculation.

Randomized Group B: Participants in the MMF arm will receive oral mycophenolate mofetil via home administration from the baseline visit (Day 1) onward. MMF will be titrated by Week 4 to a target dose of 1200 mg/m^2/day (maximum 2 g/day), given in two divided doses (600 mg/m^2 BID). See Appendix A10–2 for complete details on MMF dosing.

- The body surface area (BSA)based target dose may be rounded to the nearest 500mg dose.
- MMF should continue to be administered daily for at least 12 months until the Week 52 study visit, after which time it must be discontinued or tapered over the subsequent 3 months by Week 64.

In order to reduce the frequency and severity of infusion-related reactions, the following pre-medications will be administered prior to obinutuzumab infusions:

- Methylprednisolone: 80 mg (or 1.5 mg/kg if ≤ 45 kg) administered by slow IV infusion
- [redacted]

- Diphenhydramine hydrochloride: 0.5–1 mg/kg (rounded to the nearest available pill formulation, maximum dose 50 mg PO or intravenous equivalent, or equivalent dose of a similar agent by mouth or in accordance with local approved labeling)

The administration of all pre-medications must be completed between 30 and 60 minutes prior to the start of each obinutuzumab infusion.

During the study period, participants who are receiving daily oral prednisone (or prednisolone equivalent) at randomization will follow the guided tapering schedule (Table 7) to reach the goal of 0 mg/day by study Weeks 4–6 (and no later than Week 8) following randomization and continue without prednisone use through Week 52.

For patients who experience a relapse whilst in the study, the use of rescue therapy (e.g., local standard of care medications, other treatment or procedure for INS) is permitted at the investigator's discretion, and patients may be treated according to the investigator's best medical judgment.

[redacted]

- [redacted]

[redacted]

- First-morning void UPCR >2 g/g or
- Dipstick UA ≥3+ for 3 consecutive days (home-monitoring) and the most recent urine sample in the 3 day period determined to have UPCR >0.2 g/g as measured by the central laboratory or
- Dipstick UA protein ≥3+ on any single day with edema and urine sample determined to have UPCR >0.2 g/g as measured by the central laboratory

[redacted] However, the urine collection for UPCR central measurement should be collected before the initiation of relapse therapy. The site must review the UPCR result expeditiously after receipt from the central laboratory. [redacted]

Post-Week 52 Extension Period

Post the Week 52 visit, participants will follow the Schedule of Activities according to Table 2, until the CCOD or early study withdrawal, whichever comes first. Therefore participants who have completed their Week 52 visit will continue to be followed according to Table 2 until the last participant randomized reaches their Week 52 visit. From Week 52, MMF must be discontinued or tapered over the subsequent 3 months unless the participant experiences a protocol-defined relapse.

Participants, whether in the MMF or obinutuzumab arms, who exhibit relapse after Week 52 will be treated as per the best judgment of the investigator and this may include administration of [redacted]

Patients who do not meet the criteria for relapse on or after Week 52 will not be eligible for [redacted] in the extension period, but should continue to be followed every 3 months at study visits until CCOD.

To be eligible for [redacted] on or after Week 52, participants must meet one of the following criteria for relapse requiring treatment:

- First-morning void UPCR > 2g/g **or**
- Dipstick UA ≥ 3+ for 3 consecutive days (home-monitoring) and the most recent urine sample determined to have UPCR > 0.2 g/g as measured by the central laboratory **or**
- Dipstick UA protein ≥ 3+ on any single day with edema and urine sample determined to have UPCR > 0.2 g/g as measured by the central laboratory

[redacted]

At the time of the primary analysis (when the last participant completes the Week 52 study visit) participants are considered to have completed the study if it has been at least 12 months since their last obinutuzumab infusion and peripheral CD19 B-cell count has returned to pre-treatment values or to within the central laboratory normal range for this patient population, whichever is lower OR the patient did not receive obinutuzumab.

Participants with peripheral B-cell depletion will continue to be followed in SFU every 12 weeks for 6 months, then every 6 months thereafter until return of peripheral CD19 B cells to the pre-treatment value or to within the central laboratory normal range for this patient population, whichever is lower, until the end of study.

Safety Follow-up

Patients will enter the SFU schedule of activities specified in Table 4 for any of the following:

- At time of early withdrawal, or
- At the time of the CCOD, or
- If the sponsor terminates the study

The first SFU visit will be scheduled approximately 12 weeks after the last study visit in the treatment period or CCOD, whichever occurs first. No obinutuzumab infusions or MMF will be provided during SFU. Standard-of-care therapies may be provided at the investigator's discretion.

Duration of Participation

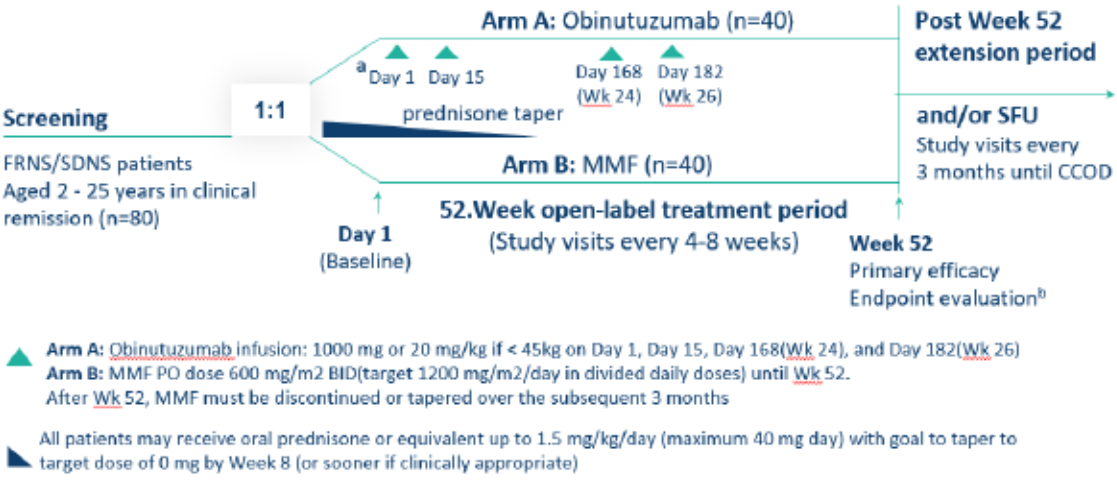
The minimum duration of study participation for each individual is expected to be approximately 1.5–2 years (SFU will be a minimum of 12 months after the last obinutuzumab infusion, for all patients who have received obinutuzumab). *Participants may continue to participate in the study and be followed up or receive repeat treatment according to the Schedule of Activities until the last participant recruited has participated in the study for at least 18 months. The maximum duration of study participation is estimated to be approximately 3 years, or longer if peripheral B cells remain below LLN at the clinical cut-off. In this case, participants will be required to return for SFU visits every 12 weeks for 6 months, then every 6 months thereafter until B cells return to pre-obinutuzumab dose baseline or the central laboratory LLN of normal for the participant's population, or until the study ends as defined in Section 4.4.*

Committees

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

1.2 STUDY SCHEMA

Figure 1 Study Schema



BID = twice a day; CCOD = common close-out date for the primary analysis; FRNS = Frequent Relapsing Nephrotic Syndrome; MMF = Mycophenolate Mofetil; PO = by mouth; orally; SDNS = Steroid Dependent Nephrotic Syndrome; SFU = safety follow-up; Wk = week.

[a] Administration of the first dose of study treatment (Day 1) should occur within 24 hours following the baseline assessments. However, administration up to 72 hours will be allowed when necessary. The second infusion should occur on Day 15±1 day.

[b] The primary efficacy endpoint of Proportion of Participants with Sustained Complete Remission at one year (see Table 5) will be measured at Week 52.

1.3 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION SCHEDULE

Table 1 Schedule of Activities for Initial Treatment Period (Screening to Week 52)

	Screening [a]	Study Visits												Unscheduled Visit [b]	
Week(s)	–4 to –1	0	2 [c]	4	8	12	20	24	26 [c]	32	40	48	52 [d]		Early Study Discontinuation
Study Day(s)	–28 to –1	1	15	28	56	84	140	168	182	224	280	336	364	NA	
Informed consent	x														
Demographics (age, sex, and self-reported race/ethnicity)	x														
Medical history, previous medications, and baseline conditions	x														
Inclusion/exclusion criteria review/confirmation	x	x													
IxRS	x [e]	x [e]	*x*	x		x	*x*	x	*x*	x	*x*	x	x		x
Participant reported outcomes: PedsQL-Fatigue; PedsQL-Quality of Life Inventory, CureGN Edema Scale, and SGA [f]															
Supplemental Questionnaire for Fatigue and Physical Functioning													*x*		
Clinician reported outcomes (PGA)															
Vital signs [g]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Weight [h]		x				x		x			x		x	x	x
Height [h]		x				x		x			x		x	x	x

Table 1 Schedule of Activities for Initial Treatment Period (Screening to Week 52) (cont.)

	Screening [a]	Study Visits												Unscheduled Visit [b]	Early Study Discontinuation
Week(s)	–4 to –1	0	2 [c]	4	8	12	20	24	26 [c]	32	40	48	52 [d]		
Study Day(s)	–28 to –1	1	15	28	56	84	140	168	182	224	280	336	364	NA	
Complete physical examination [i]	x													x [i]	
Limited physical examination [j]		x						x					x		x
Chest X-ray [k]	x														
ECG (12-lead)	x														
Hematology *(CBC)* [l]	x	x	x	x		x	x	x	x	x			x	x [m, n]	x
HIV and TB [o]	*x*														
Local laboratory CBC and coagulation panel														*x* [p]	
Chemistry [q]	x	x	x	x		x	x	x	x	x			x	x [m, n]	x
Pregnancy test (serum) [r]	x														
Pregnancy test (urine) [r]		x	x	x	x	x	x	x	x	x	x	x	x		
UA [s]	x	x		x	x	x	x	x		x	x	x	x	x [m, n]	x
Urine dipstick daily home monitoring with central-lab UPCR as needed [t]	←												→		
Central-lab UPCR [u]	x [v]					x		x			x		x		x
HBsAg, HBcAb, and HCV serology	x														
Quantitative serum Ig levels	x	x				x		x		x			x	x [n]	x
Blood sample for flow cytometry [w]		x		x				x		x			x	x [n]	x

Table 1 Schedule of Activities for Initial Treatment Period (Screening to Week 52) (cont.)

	Screening [a]	Study Visits												Unscheduled Visit [b]	Early Study Discontinuation
Week(s)	–4 to –1	0	2 [c]	4	8	12	20	24	26 [c]	32	40	48	52 [d]		
Study Day(s)	–28 to –1	1	15	28	56	84	140	168	182	224	280	336	364	NA	
High-sensitivity flow cytometry [w]		x	x	x		x		x		x			x	x [n]	x
Serum PK sample [x, y]		x	x	x		x		x	x	x			x	x [n]	x
[redacted]															
Concomitant medications [z]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [aa]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Obinutuzumab administration [bb]		x [cc]	x					x	x						
MMF dispensing [dd]		x		x		x	x	x		x	x	x	x [ee]		
Prednisone taper [ff]			x	x	x										
Evaluation of relapse and edema [ss]	←												→	*x*	

[redacted] BSA=body surface area; *CBC = complete blood count*; CCOD=common close-out date; CPK=creatinine phosphokinase; CT=computed tomography; CureGN=Cure Glomerulonephropathy; eCRF=electronic Case Report Form; FMV=first-morning void; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; *HIV=human immunodeficiency virus*; IxRS=interactive voice or web-based response system; MMF=mycophenolate mofetil; NA=not applicable; PedsQL-Fatigue=Pediatric Quality of Life Inventory-Multidimensional Fatigue Scale; PGA=Physician's Global Assessment; PK=pharmacokinetic; PO=orally; SGA=Subject's Global Assessment; *TB=tuberculosis;* UA=urinalysis; UPCR=urinary protein-to-creatinine ratio.

Notes: Individuals who do not meet the criteria for participation in this study may qualify for one full re-screening (for a total of two screenings per individual) at the investigator's discretion.

All assessments and laboratory sampling should be performed within 3 days of the scheduled visit, unless otherwise specified.
On obinutuzumab treatment days, all assessments, including blood collection, should be performed prior to any protocol-mandated intervention, i.e., prior to pre-medications, unless otherwise specified.

All study visits except for Day 1 (baseline), Day 15 (±1 day), Day 168 (±1day), and Day 182 (±1day) should be performed within ±3 days of the scheduled visit, or as otherwise noted in protocol.

Table 1 Schedule of Activities for Initial Treatment Period (Screening to Week 52) (cont.)

Participants will undergo the specified assessments, and additional assessments may be performed during an unscheduled visit if clinically indicated, as determined by the investigator. *All efforts should be made to obtain the laboratory tests associated with each study visit. In extenuating circumstances, the following laboratory tests should be prioritized: chemistry, hematology (CBC), UA, central-lab UPCR, high-sensitivity flow cytometry, and serum PK sample.*

Study Day 1=baseline and randomization visit.

[a] Screening should ideally be completed within 28 days prior to randomization. The screening window may be extended by 7 days if required in case of unavoidable delay in screening assessments.

[b] Unscheduled visits can occur at any time in the study, including upon relapse. *The relapse form in the eCRF must be completed for unscheduled visits occurring in the setting of confirmed or suspected relapse.*

[c] Week 2 visit is for participants randomized to obinutuzumab and for participants randomized to MMF who are newly initiating MMF (not yet titrated to target dose) at study onset. For participants randomized to MMF, obinutuzumab administration or PK sampling is not required at Week 2. Week 26 visits are for participants randomized to obinutuzumab only.

[d] Week 52 is the primary endpoint analysis. The primary analysis will occur when all participants have either completed the Week 52 study visit and assessments, withdrawn early or had intercurrent events prior to Week 52. For patients with fever or signs/symptoms of infection, the Week 52 visit should be deferred for up to 2 weeks until fever and signs/symptoms of infection have resolved.

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

[f] Participant-reported outcomes will be performed prior to other assessments and procedures.

[g] Vital signs (blood pressure and pulse rate (while participant is seated), respiratory rate, and body temperature) are required for all participants per the Schedule of Activities. On obinutuzumab infusion administration days, (for those participants randomized to Arm A), vital signs should be taken pre-infusion, then every 15 minutes for 1 hour, then every 30 minutes until the end of the infusion, and then every 30 minutes post-infusion for at least 2 hours after the first infusion (or for 30 minutes after subsequent infusions) is completed until the IV line is removed. Additional readings may be obtained at the discretion of the investigator.

[h] The BSA calculation should be performed whenever weight and height measurements are taken to inform BSA-based MMF or weight-based obinutuzumab dosing (20 mg/kg for participants <45 kg), as applicable.

[i] 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. Complete physical examination may also be considered during an unscheduled visit at the investigator's discretion.

[j] Limited, symptom-directed physical examinations should be performed at *baseline,* specified post-baseline visits, and as clinically indicated. Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

Table 1 Schedule of Activities for Initial Treatment Period (Screening to Week 52) (cont.)

[k] For children < 12 years old, chest X-ray should be performed only if clinically indicated/relevant based on laboratory/clinical work up. For patients 12 years of age or older, if a chest X-ray or CT scan of the chest has been obtained within the past 3 months prior to screening and no new pulmonary signs, symptoms or clinically significant abnormalities were present that, in the investigator's judgment, would preclude participation in the study, a chest X-ray is not required.

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

[m] Hematology, chemistry and/or UA assessments should be performed as part of unscheduled visits only if clinically indicated (e.g., if the unscheduled visit is being done as part of an assessment of an adverse event for which such labs would be relevant) or if meeting criteria specified in subsequent footnote.

[n] Hematology, chemistry, UA, serum Ig, flow cytometry, high sensitivity flow cytometry, and serum PK assessments should only be performed as part of unscheduled visits if these laboratories were specified to be performed as part of the previously scheduled visit but were not performed for any reason OR if clinically indicated in the judgment of the investigator.

[o] *HIV and TB testing will be performed at baseline ONLY if required by local regulations.*

[p] *An initial cohort of participants in the obinutuzumab arm will undergo additional local laboratory testing (CBC and coagulation panel, including Prothrombin Time and International Normalized Ratio (PT-INR) and Prothrombin Time Test (PTT)) at one time point between Day 7 and the second infusion of obinutuzumab, specified to occur on Day 15. These laboratory tests (CBC and coagulation panel) may be obtained on the same day as the second obinutuzumab infusion as long as the results are evaluated by the investigator prior to the administration of the second dose of obinutuzumab. Local CBC or coagulation laboratory results need to be reported as laboratory results under an unscheduled visit. These patients who will receive additional local laboratory testing will be identified by the IRT system. Approximately 10 participants in the obinutuzumab arm will be selected for this additional local laboratory testing; the exact number of participants will depend upon review of the clinical data obtained.*

[q] Serum chemistry panel includes: albumin, alkaline phosphatase, ALT, AST, bicarbonate, calcium, chloride, cholesterol, creatinine, creatinine kinase, direct bilirubin, GGT, globulin, random glucose, indirect bilirubin, lactate dehydrogenase magnesium, phosphorus, potassium, sodium, total bilirubin, total protein, triglycerides, blood urea nitrogen, and uric acid.

[r] *Pregnancy tests are only indicated* for females of childbearing potential, including those who have had a tubal ligation. Positive *urine pregnancy* test results will be confirmed with a serum pregnancy test *and* study drug must not be administered unless the serum pregnancy test result is negative.

[s] All urinalyses collected at study visits per the Schedule of Activities will be analyzed at the central laboratory and include microscopic examination and macroscopic UA. See Appendix 8 for instructions on collection of urine samples on study visit days.

Table 1 Schedule of Activities for Initial Treatment Period (Screening to Week 52) (cont.)

[t] All participants will be required to perform daily UA (UA dipstick test) at home to monitor for evidence of proteinuria relapse; UA ≥ 3+ for 3 consecutive days (daily home monitoring) **or** UA protein ≥ 3+ on any single day with edema (swelling). In the event of relapse, the most recent available urine sample (e.g., the third day) qualifying the relapse (or in the case of edema, the single qualifying urine sample when edema is noticed) will also be analyzed by urine protein:creatinine ratio (UPCR) at a central laboratory to confirm the relapse status. These UPCR values will be compared between the 2 arms of the study to assess the validity of parental home-monitoring and, in the case of relapse, correlation with UA dipstick analysis. See Appendix 9 for further instructions on collecting FMV urine samples at home.

[u] For all visits requiring a central laboratory UPCR assessment (screening, Week 12, Week 24, Week 40, Week 52 and early study discontinuation) a FMV urine sample is required. If a FMV urine sample cannot be collected or if the UPCR result is greater than 0.2 g/g in absence of a relapse for these visits, participants must provide a first-morning urine sample for repeat analysis on a subsequent day, up to 2 weeks after the clinic visit. See Appendix 8 for instructions on collection of FMV urine samples on study visit days.

[v] Potential participants must be in complete remission defined by the absence of edema, first-morning void UPCR ≤ 0.2 g/g at screening and have 3 consecutive daily home urine dipstick readings of trace or negative for protein within the week prior to randomization.

[w] Samples will be drawn prior to administration of protocol-required treatment (including IV methylprednisolone, antihistamines, and study drug infusions) on dosing days.

[x] At obinutuzumab infusion visits, obtain pre-infusion *serum PK samples* simultaneously with the earlier blood draw [prior to premedication] for the sake of patient comfort. *Obtain post-*infusion *serum PK samples* 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.

[y] Serum PK and [redacted] are only to be collected in participants receiving obinutuzumab treatment.

[z] Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, nutritional supplements) used by a participant 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.

[aa] 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.**

[bb] At infusion visits, premedication with methylprednisolone 80 mg IV (or 1.5 mg/kg if ≤45 kg), [redacted] and diphenhydramine 0.5–1 mg/kg (rounded to the nearest available pill formulation, maximum dose 50 mg) PO (or equivalent dose of a similar agent) will be given. The administration of these pre-medications should be completed between 30 and 60 minutes prior to the study drug infusion.

[cc] Administration of the first dose of study treatment (Day 1) should occur within 24 hours following the baseline assessments; however, administration up to 72 hours will be allowed when necessary. The second infusion should occur on Day 15 ± 1 day.

[dd] For all sites, IxRS will be contacted in order to confirm MMF dispensing out of the central supply for participants receiving MMF.

[ee] From the Week 52 visit onwards, MMF must be discontinued or tapered over the subsequent 3 months.

Table 1 Schedule of Activities for Initial Treatment Period (Screening to Week 52) (cont.)

[ff] Participants may initiate oral prednisone (or equivalent corticosteroid) at a dose of up to 1.5 mg/kg/day (maximum, 40 mg/day) during screening and remain at this dose until the Week 2 visit. The prednisone taper will begin on Day 15, as clinically indicated to achieve a target prednisone (or equivalent) dose of 0 mg/day by Week *6* (or sooner, if appropriate, and no later than Week *8*). Oral prednisone will be withheld on all days when pre-infusion methylprednisolone is given.

[ss] *Patient diaries will prompt participants to contact study sites in the event of either: 1) UA dipstick protein ≥ 3 ± on any single day with edema (swelling); or 2) three consecutive days of UA dipstick protein ≥ 3 ±. Sites should advise participants to contact the site in the event of each of the above scenarios. The relapse form in the eCRF must be completed as close to the time of suspected relapse as possible.*

Table 2 Schedule of Activities for Extension Period (After Week 52 to Week 148+)

	Treatment Extension Study Visits								Unscheduled Visit	
Week(s)	64	76 [a]	88	100	112	124	136	148 [b]		Early Study Discontinuation
Study Day(s)	448	532	616	700	784	868	952	1036	NA	
Participant-reported outcomes (PedsQL-Fatigue Scale, PedsQL Quality of Life Inventory, CureGN Edema Scale, and SGA) [c]										
Clinician-reported outcomes (PGA)										
Vital signs [d]	x	x	x	x	x	x	x	x	x	
Weight [e]	x	x	x	x	x	x	x	x		x
Height [e]	x	x	x	x	x	x	x	x		
Limited physical examination [f]	x			x			x			x
Hematology [g]	x	x	x	x	x	x	x	x	x [h, i]	x
Chemistry [j]	x	x	x	x	x	x	x	x	x [h, i]	x
Pregnancy test (urine) [k]	x	x	x	x	x	x	x	x		
UA [l]	x	x	x	x	x	x	x	x	x [h, i]	x
Urine dipstick daily home monitoring with central-lab UPCR as needed [m]	←							→		
Central-lab UPCR [n]		x								x
Quantitative serum Ig levels		x		x		x		x	x [i]	x
Blood sample for flow cytometry [o]										
High-sensitivity flow cytometry [o]										
Concomitant medications [p]	x	x	x	x	x	x	x	x	x	x

Table 2 Schedule of Activities for Treatment Extension (After Week 52 to Week 148+) (cont.)

	Treatment Extension Study Visits								Unscheduled Visit	
Week(s)	64	76 [a]	88	100	112	124	136	148 [b]		Early Study Discontinuation
Study Day(s)	448	532	616	700	784	868	952	1036	NA	
Adverse events [q]	x	x	x	x	x	x	x	x	x	x

[redacted] BSA=body surface area; CCOD=common close out date; CureGN=Cure Glomerulonephropathy; eCRF=electronic Case Report Form; FMV=first-morning void; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; IxRS=interactive voice or web-based response system; MMF=mycophenolate mofetil; NA=not applicable; PedsQL-Fatigue=Pediatric Quality of Life Inventory-Multidimensional Fatigue Scale; PGA=Physician's Global Assessment; SGA=Subject's Global Assessment; UA=urinalysis; UPCR=urinary protein-to-creatinine ratio.

Notes: All study visits should be performed within ±3 days of the scheduled visit. Participants will undergo the specified assessments, and additional assessments may be performed during *unscheduled visits* if clinically indicated, as determined by the investigator.

[a] For patients with fever or signs/symptoms of infection, the Week 76 visit should be deferred for up to 2 weeks until fever and signs/symptoms of infection have resolved.

[b] After Week 148, study visits should continue to be scheduled every 12 weeks until CCOD.

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

[d] Vital signs (blood pressure and pulse rate (while participant is seated), respiratory rate, and body temperature) are required for all participants per the Schedule of Activities.

[e] BSA calculation should be performed whenever weight and height measurements are taken to inform BSA-based MMF dosing.

[f] 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 participant notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

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

[h] Hematology, chemistry and/or UA assessments should be performed as part of unscheduled visits only if clinically indicated (e.g., if the unscheduled visit is being done as part of an assessment of an adverse event for which such labs would be relevant) or if meeting criteria specified in subsequent footnote.

[i] Hematology, chemistry, UA, serum Ig, flow cytometry, and high sensitivity flow cytometry assessments should only be performed as part of unscheduled visits if these laboratories were specified to be performed as part of the previously scheduled visit but were not performed for any reason OR if clinically indicated in the judgment of the investigator.

Table 2 Schedule of Activities for Treatment Extension (After Week 52 to Week 148+) (cont.)

[j] Serum chemistry panel includes albumin, alkaline phosphatase, ALT, AST, bicarbonate, calcium, chloride, cholesterol, creatinine, creatinine kinase, direct bilirubin, GGT, globulin, random glucose, indirect bilirubin, lactate dehydrogenase magnesium, phosphorus, potassium, sodium, total bilirubin, total protein, triglycerides, urea nitrogen, and uric acid.

[k] Only for females of childbearing potential, including those who have had a tubal ligation, positive test results will be confirmed with a serum pregnancy test. Study drug infusion must not be administered unless the serum pregnancy test result is negative.

[l] All urinalyses collected at study visits per the Schedule of Activities will be analyzed at the central laboratory and include microscopic examination and macroscopic UA. See Appendix 8 for instructions on collection of urine samples on study visit days.

[m] All participants will be required to perform daily UA (UA dipstick test) at home to monitor for evidence of proteinuria relapse; UA ≥3+ for 3 consecutive days (daily home monitoring) **or** UA protein ≥3+ on any single day with edema (swelling). In the event of relapse, the most recent available urine sample (e.g., the third consecutive day) qualifying the relapse (or in the case of edema, the single qualifying urine sample) will also be analyzed by urine protein:creatinine ratio (UPCR) at a central laboratory to confirm the relapse status. These UPCR values will be compared between the 2 arms of the study to assess the validity of parental home-monitoring and, in the case of relapse, correlation with UA dipstick analysis. See Appendix 9 for further instructions on collecting FMV urine samples at home.

[n] For all visits requiring a central laboratory UPCR assessment, a FMV urine sample is required. If a FMV urine sample cannot be collected for Week 76 or if the UPCR result is greater than 0.2 g/g in absence of a relapse, participants must provide a first-morning urine sample for repeat analysis on a subsequent day, up to 2 weeks after the clinic visit. See Appendix 8 for instructions on collection of FMV urine samples on study visit days.

[o] Samples will be drawn prior to administration of protocol-required treatment (including IV methylprednisolone, antihistamines, and study drug infusions) on dosing days.

[p] Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, nutritional supplements) used by a participant 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.

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

Table 3 Schedule of Activities for Obinutuzumab Administration as Rescue Therapy or Post-Week 52 Repeat Treatment

Obinutuzumab treatment regimen consists of 2 infusions (Infusion 1 and Infusion 2 (given 14 days apart). Upon completion of Infusion 2 in this Schedule of Activities, whether for rescue therapy or as post-Week 52 repeat treatment for patients randomized to obinutuzumab, participants will continue to follow with their next study scheduled visit according to Table 1 or Table 2, as applicable.		
	Infusion 1	Infusion 2
Day	1	15 (±1)
IxRS [a]	x	x
Participant-reported outcomes (PedsQL-Fatigue Scale, PedsQL Quality of Life Inventory, CureGN Edema Scale, and SGA) [b]	x	
Clinician-reported outcomes (PGA)	x	
Vital signs [c]	x	x
Weight [d]	x	
Height [d]	x	
Hematology [e]	x	x
Chemistry [f]	x	x
Pregnancy test (urine) [g]	x	x
Urinalysis [h]	x	
Blood sample for flow cytometry [i]	x	x
High-sensitivity flow cytometry [i]	x	x
Serum PK sample [j]	x	x
[redacted]		
Concomitant medications [k]	x	x
Adverse events [l]	x	x

[redacted] BSA=body surface area; FMV=first-morning void; IxRS=interactive voice or web-based response system; PedsQL-Fatigue=Pediatric Quality of Life Inventory-Multidimensional Fatigue Scale; PGA=Physician's Global Assessment; CureGN=Cure Glomerulonephropathy PK=pharmacokinetic; SGA=Subject's Global Assessment; UPCR=urinary protein-to-creatinine ratio.

On obinutuzumab treatment days, all assessments, including blood collection, should be performed prior to any protocol-mandated intervention, i.e., prior to pre-medications, unless otherwise specified. Where participant-reported outcomes or blood collection assessments have been performed in the past 7 days, there is no requirement to repeat during obinutuzumab administration visits.

In the case where obinutuzumab administration occurs on a scheduled study visit, the Schedule of Activities per Table 3 should be followed together with any assessments that are required in addition for the scheduled visit.

[a] For obinutuzumab rescue therapy or repeat treatment, IxRS will be contacted to obtain drug assignment.

[b] Participant-reported outcomes will be performed prior to other assessments and procedures.

Table 3 Schedule of Activities for Obinutuzumab Administration as Rescue Therapy or Post-Week 52 Repeat Treatment (cont.)

[c] Blood pressure and pulse rate (while participant is seated, respiratory rate, and body temperature. Vital signs should be taken pre-infusion, then every 15 minutes for 1 hour, then every 30 minutes until the end of the infusion, and then every 30 minutes post-infusion for at least 2 hours after the first infusion (or for 30 minutes after subsequent infusions) is completed until the IV line is removed. Additional readings may be obtained at the discretion of the investigator.

[d] The BSA calculation should be performed whenever weight and height measurements are taken to inform weight-based obinutuzumab dosing (20 mg/kg for participants <45 kg), as applicable.

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

[f] Serum chemistry panel includes: albumin, alkaline phosphatase, ALT, AST, bicarbonate, calcium, chloride, cholesterol, creatinine, creatinine kinase, direct bilirubin, GGT, globulin, random glucose, indirect bilirubin, lactate dehydrogenase magnesium, phosphorus, potassium, sodium, total bilirubin, total protein, triglycerides, urea nitrogen, uric acid.

[g] Only for Females of childbearing potential, including those who have had a tubal ligation, positive test results will be confirmed with a serum pregnancy test. Study drug must not be administered unless the serum pregnancy test result is negative.

[h] All urinalyses collected at study visits per the Schedule of Activities will be analyzed at the central laboratory and include microscopic examination and macroscopic urinalysis. See Appendix 8 for instructions on collection of urine samples on study visit days.

[i] Samples will be drawn prior to administration of protocol-required treatment (including IV methylprednisolone, antihistamines, and study drug infusions) on dosing days.

[j] 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.

[k] Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, nutritional supplements) used by a participant 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.

[l] For obinutuzumab 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.

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

Patients who have not received obinutuzumab will be seen for only a single safety follow-up visit, with assessments specified in SFU Visit 1.

Patients who have received obinutuzumab will be followed in SFU until such patients have fulfilled both of the following criteria:

1. Peripheral B cells have returned to pre-obinutuzumab baseline levels or to within the normal range for the population, whichever is lower.
2. The last infusion of obinutuzumab was at least 12 months ago.

Patients who have received obinutuzumab but who have not fulfilled both of the following criteria will be followed until the end of study, defined as the date when the last participant last visit (LPLV) occurs. The LPLV will occur when the last participant enrolled completes the SFU requirements, up to a maximum of 18 months from the last obinutuzumab infusion.

For example, for a patient who had received obinutuzumab 7 months before the initiation of SFU, such a patient would be seen at SFU Visit 1, approximately 12 weeks after the start of the SFU and 10 months after that patient's last infusion of obinutuzumab. Such a patient would again be seen at SFU Visit 2, approximately 12 weeks after that patient's first SFU visit. If at the SFU Visit 2, that patient's peripheral B cells had returned to pre-obinutuzumab baseline levels or to within the normal range for the population, whichever is lower, this SFU Visit 2 would be the patient's last study visit.

		SFU		
	SFU Visit 1	SFU Visit 2	SFU Visit 3	Continued SFU Visits
Week of SFU	12 (±1week)	24 (±1week)	52 (±1 week)	Continued Follow-Up Visits Every 6 Months (if needed) [a]
Urinalysis [b]	x	x	x	x
Pregnancy test (urine) [c]	x	x	x	x
Quantitative serum Ig levels [d]	x	x	x	x
[redacted]				
Concomitant medications [e]	x	x	x	x
Adverse events [f]	x	x	x	x

eCRF=electronic Case Report Form; SFU=safety follow-up; UPCR=urinary protein-to-creatinine ratio.

[a] For participants whose peripheral B cells remain depleted, follow-up visits will continue to be scheduled every 6 months until peripheral B-cell counts have returned to pre-obinutuzumab baseline levels or to within the normal range for the population, whichever is lower, or until the study end date, as defined in Section 4.4, whichever is sooner.

[b] First morning void (FMV) urine sample is preferred. All urinalyses will be analyzed at the central laboratory and include microscopic examination and macroscopic urinalysis. The first SFU visit will also assess UPCR as assessed by central laboratory.

[c] Only for females of child-bearing potential. Pregnancy tests should be repeated as clinically required. A positive test result will be confirmed with a serum pregnancy test.

[d] Total Ig, IgG, IgA, and IgM.

[e] During the SFU period, reporting of concomitant medications should be limited to subsequent treatments for nephrotic syndrome, use of biologics, immunosuppressive medications, and cell-depleting agents. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

[f] For all serious infectious adverse events reported, CBC with differential, quantitative immunoglobulins, and flow cytometry should be measured within 1 week of onset. Pregnancy information will be reported for the duration of the SFU period.

2. INTRODUCTION

2.1 STUDY RATIONALE

The purpose of this open-label, randomized multicenter study is to assess the efficacy, safety, and pharmacokinetics (PK)/pharmacodynamics (PD) of obinutuzumab compared with mycophenolate mofetil (MMF) in participants (aged ≥2–25 years old) with childhood-onset frequently relapsing nephrotic syndrome (FRNS) or steroid dependent nephrotic syndrome (SDNS).

Patients with childhood onset FRNS/SDNS are at risk of short-term and long-term steroid toxicity, severe infections, edema, thromboembolic events, and acute kidney injury during relapses. The reduction of these risks is dependent on the identification of effective therapy and the maintenance of clinical remission via sustained reduction in proteinuria. Current standard of care remains limited to a combination of systemic corticosteroids and immunosuppressive therapies, but most available regimens confer a complete renal response and remission in fewer than half of treated patients.

2.2 BACKGROUND

Childhood-onset idiopathic nephrotic syndrome (INS) is also known as primary nephrotic syndrome (excluding secondary causes) and encompasses minimal change disease (MCD) and focal and segmental glomerulosclerosis (FSGS). Although the disease is rare, the incidence of childhood-onset INS varies by ethnicity and region and is higher among certain ethnic groups, specifically South Asians and African-Americans, where the influence of genetic factors confers a higher risk, particularly for FSGS (Chanchlani and Parekh 2016). The disease is usually first diagnosed between 2 and 5 years of age (in 70% of patients with MCD), typically affects more boys than girls (2:1), and is defined by the presence of nephrotic-range proteinuria, edema, hyperlipidemia, and hypoalbuminemia (Noone et al. 2018).

Patients with childhood-onset INS are initially treated with systemic oral corticosteroids. The frequency of relapses and response to corticosteroid treatment permits the classification of the disease into subtypes reflecting disease severity. These subtypes include "steroid-resistant nephrotic syndrome (underlying genetic cause)," "non/infrequent relapsing steroid sensitive nephrotic syndrome, " "FRNS," and "SDNS" (Noone et al. 2018). In the latter two subtypes, patients receive multiple courses of steroids during episodes and often continue receiving steroid maintenance therapy to prevent further relapses. The optimal goal of treatment is maximal steroid sparing while

limiting the relapse rate based on the patient's clinical response and drug-related adverse effects.

Childhood-onset INS recurs in more than 75% of patients and almost 50% of patients show frequent relapses or steroid dependency (Abdel-Hafez et al. 2017). Among children whose disease cannot be controlled well with steroids, a number of steroid-sparing immunosuppressive agents (e.g., cyclophosphamide, levamisole, cyclosporin A, tacrolimus, MMF, and rituximab) have been shown to reduce the risk of relapse. However, high-quality head-to head data comparing these agents are limited (Mason et al. 2020).

Despite current treatments, patients remain at significant risk for impaired growth and other significant side effects of steroid-related toxicity. Given the frequent clinical relapse rates following the use of immunosuppressant therapies and the associated potential risk of end-stage kidney disease in childhood-onset INS, there remains an unmet need for approved steroid-sparing therapies with improved efficacy and better long-term outcomes.

The anti-CD20 monoclonal antibody rituximab was first described for the treatment of childhood-onset INS in 2004 (Benz et al. 2004), and has since emerged as a promising unapproved treatment option in both children and adults with FRNS or SDNS. A number of investigator-initiated trials and case reports of its use have been described in the literature and clinical response rates vary (from 50%–85% of patients in renal remission at 12 months [no relapse]) and rituximab has been shown to reduce the annual rate of relapse in patients with FRNS and SDNS. However, patients who do not achieve complete remission at 12 months generally relapse between 8 and 9 months after rituximab treatment, and these relapses mostly occur in the context of B-cell recovery/reconstitution (Iijima et al. 2014; Colucci et al. 2016). It is hypothesised that anti-CD20 therapy may be disease-modifying and could have a direct impact on immunological memory in children with FRNS or SDNS. Delayed reconstitution of the memory B-cell pool is associated with a prolonged remission despite tapering or discontinuation of concomitant immunosuppression (Colucci et al. 2019). Obinutuzumab (GAZYVA®, GAZYVARO®) is a humanized, glycoengineered type II anti-CD20 antibody with enhanced depletion of B cells from peripheral blood and tissue relative to type I antibodies such as rituximab and ofatumumab. It is administered as an IV infusion. Consistent with its more potent B-cell depletion, obinutuzumab was superior to rituximab for the treatment of chronic lymphocytic leukemia (CLL) and follicular lymphoma (FL) in adults when administered in combination with standard chemotherapy and is currently approved worldwide in these indications. Obinutuzumab is also indicated for the treatment of patients with FL who did not respond to, or who progressed during or after treatment with, rituximab or a rituximab-containing regimen. In addition, obinutuzumab is currently in clinical development for adult and pediatric autoimmune diseases (lupus nephritis [LN], membranous nephropathy, and systemic lupus erythematosus [SLE]).

The proposed use of obinutuzumab for the treatment of childhood-onset INS is based on the clinical efficacy observed with other B cell depleting therapies (e.g., rituximab and ofatumumab). Obinutuzumab has enhanced B-cell depletion compared with rituximab and other type I anti-CD20 molecules as a result of its humanized glycoengineering and Type II binding conformation, which confer greater direct cell death, reduced internalization, and lower complement-dependent cytotoxicity (Mössner et al. 2010; Herter et al. 2013). Obinutuzumab has been shown to be superior to rituximab in depleting B cells in blood and tissue. The proposed hypothesis is that greater B cell depletion can lead to improved clinical efficacy compared with rituximab and other B cell therapies in the treatment of childhood-onset INS.

Detailed information on obinutuzumab is provided in the obinutuzumab Investigator's Brochure.

2.3 BENEFIT–RISK ASSESSMENT

The purpose of this study is to assess the efficacy, safety, and PK/PD of obinutuzumab compared with MMF in participants (aged between ≥2 and ≤25 years old) with childhood-onset FRNS or SDNS. The goals of therapy in childhood-onset idiopathic nephrotic syndrome are rapid induction of renal remission, prevention of irreversible kidney damage, proteinuria relapse prevention, and limitation of therapy-related toxicity. The current standard of care for FRNS and SDNS does not routinely confer sustained renal remission or prevent frequent proteinuria relapses. Furthermore, current standard-of-care regimens are associated with a number of significant well-described toxicities.

Based on the similarities of other renal diseases under study with obinutuzumab and therapy response, it is expected that the benefit–risk profile of obinutuzumab will be qualitatively similar in the childhood-onset nephrotic syndrome population if similar PK drug exposures and PD effects (B-cell depletion) are achieved. Obinutuzumab results in a greater degree of B-cell depletion in peripheral blood and tissues compared with the Type I anti-CD20 monoclonal antibody rituximab (Mössner et al. 2010).

Potential side effects related to this mechanism of action include, but are not limited to, neutropenia, thrombocytopenia, and hypogammaglobulinemia. B-cell depletion and/or neutropenia may affect the incidence and severity of infections in patients receiving obinutuzumab. The long-term safety profile of prolonged B-cell depletion with obinutuzumab is still being studied in the adult and adolescent renal disease populations (LN, SLE, and membranous nephropathy), and no clinical trial data are currently available for its use in patients under the age of 18. Results from the Phase II NOBILITY Study WA29748 indicate that the long-term safety profile of obinutuzumab in adults with LN is consistent with the known safety profile of obinutuzumab in oncology indications and underlying disease of the LN patient population.

Available nonclinical and clinical data in various hematological and autoimmune indications have demonstrated that obinutuzumab, a Type II anti-CD20, induces enhanced B-cell depletion compared with rituximab. More potent B-cell depletion may provide transformative treatment, steroid-sparing, and increased efficacy and duration of response in frequently relapsing or steroid-dependent INS. Limited off-label clinical practice experience in single-center hospital settings and a retrospective French study (Dossier et al. 2020) appear to provide supportive data, albeit limited, that obinutuzumab may provide benefit in reducing proteinuria and disease relapses in patients with childhood-onset INS, further supporting the scientific rationale of a role of B-cell depletion therapy as a proposed therapeutic option in this rare, debilitating kidney disease.

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), an assessment was conducted to determine whether there is any impact of the COVID-19 vaccines on the benefit-risk assessment of this study protocol. Given the mechanism of action of obinutuzumab, it is expected that the efficacy of COVID-19 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 it is strongly recommended that where possible, COVID-19 vaccines should be administered to patients at least 28 days before they start immunosuppressive therapy. The COVID-19 vaccines may also be administered at any time during the study provided they are non-live vaccines. If administered during the study, the COVID-19 vaccines are considered concomitant medications. The COVID-19 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 COVID-19 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.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of obinutuzumab may be found in the Obinutuzumab Investigator's Brochure.

Taking into account the available efficacy data in adult patients with other renal diseases such as LN, the safety profile for obinutuzumab in hematological and autoimmune

diseases, and the risk mitigation measures for the study, the benefit–risk profile is expected to be acceptable for obinutuzumab in the setting of childhood-onset INS.

See Appendix 3 for information on anticipated risks for obinutuzumab and risk mitigation measures, including guidelines for managing adverse events associated with obinutuzumab.

3. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of obinutuzumab compared with MMF in participants aged between ≥2 and ≤25 years old with childhood-onset FRNS or SDNS. Specific objectives and corresponding endpoints for the study are outlined in Table 5.

In this protocol, "study treatment" refers to the treatments assigned to participants as part of this study (i.e., obinutuzumab or MMF).

Table 5 Objectives and Corresponding Endpoints

Primary Objective	Corresponding Endpoint
• To evaluate the efficacy of obinutuzumab compared with MMF	• Proportion of participants with sustained complete remission at 1 year, defined as first morning void UPCR ≤ 0.2 g/g at Week 52 without occurrence of a relapse or any *other* intercurrent event *as defined below.* *Participants experiencing any of the following intercurrent events occurring after Week 8 will be considered a non-responder*: 1. Relapse as defined by any of the following events [a]: a) First-morning void UPCR ≥ 2 g/g **or** b) Dipstick UA ≥ 3+ for 3 consecutive days (home-monitoring) and the most recent urine sample of the 3 day period determined to have UPCR > 0.2 g/g as measured by the central laboratory **or** c) Dipstick UA protein ≥ 3+ on any single day with edema and urine sample determined to have UPCR > 0.2 g/g as measured by the central laboratory 2. Any systemic corticosteroids usage for > 14 days in a 30 day period *Participants experiencing any of the following intercurrent events occurring after randomization will be considered a non-responder* [b,c]: 3. Initiation of any rescue therapy for INS, as determined by the investigator's best medical judgement, other than systemic corticosteroids 4. Treatment discontinuation due to lack of efficacy 5. Death

Table 5 Objectives and Corresponding Endpoints (cont.)

Secondary Objectives	Corresponding Endpoints [c]
• To evaluate the efficacy of obinutuzumab compared with MMF	• Overall *relapse-free survival* (RFS) • Probability of RFS at Week 52 • Cumulative corticosteroid dose • Number of relapses • Proportion of participants experiencing edema associated relapse *during the 52-week treatment period* [d] • Proportion of patients *with sustained complete remission at Week 76*
• To evaluate changes in fatigue of participants treated with obinutuzumab compared with MMF	• *Mean* change in "General Fatigue" domain of PedsQL-Multidimensional Fatigue scale total score from baseline to Week 52
• To evaluate changes in the quality of life of participants treated with obinutuzumab compared with MMF	• *Mean change* in "Physical Functioning" domain of PedsQL-Quality of Life Inventory from baseline to Week 52
• To evaluate edema over time	• *Mean* change in CureGN Edema Scale from baseline to Week 52
• To evaluate the safety of obinutuzumab compared with MMF	• Incidence, nature, and severity of adverse events, with severity determined according to AE intensity (mild, moderate, severe, life-threatening) and NCI CTCAE grading if applicable from baseline to Week 52 • Incidence of laboratory or vital sign abnormalities from baseline to Week 52
• To characterize the obinutuzumab PK profile	• Serum concentrations of obinutuzumab at specified timepoints
• To characterize obinutuzumab-induced PD changes	• Proportion of participants achieving B-cell depletion (HSFC) at specified timepoints • Total peripheral B cell and B cell subsets (e.g., memory B cells) counts and change from baseline at specified timepoints

Table 5 Objectives and Corresponding Endpoints (cont.)

Exploratory Objectives	Corresponding Endpoints
• [redacted]	• [redacted]
• [redacted]	• [redacted]
• [redacted]	• [redacted]

Intercurrent events are defined as above *for the primary endpoint* because such events have the potential to impact UPCR at Week 52 or because such events would themselves represent a loss of complete remission (e.g., relapse). For the complete definition of the primary endpoint and related intercurrent events, please see Section 9.5.

Relapse will be objectively measured by the assessment of proteinuria, and the urine samples that define a relapse will be confirmed by UPCR central laboratory analysis.

Relapse will be defined by any of the following events:

- First-morning void UPCR >2 g/g **or**
- Dipstick UA ≥3+ for 3 consecutive days (home-monitoring) and the most recent urine sample of the 3 day period determined to have UPCR >0.2 g/g as measured by the central laboratory **or**
- Dipstick UA protein ≥3+ on any single day with edema and urine sample determined to have UPCR >0.2 g/g as measured by the central laboratory

Maintaining sustained remission in patients with FRNS/SDNS continues to be a challenge. In this patient population, where frequent relapses on a background of oral steroids and immunosuppressants are common, the goal of any new treatment option is to effectively prevent relapse and maintain patients in complete remission. Oral corticosteroids remain the mainstay of treatment for relapse. However, the extended use of oral corticosteroids is not encouraged in situations where a steroid-sparing option may be available, particularly in children who remain at risk for impaired growth and other significant side effects of steroid-related toxicity. With accumulating data on the efficacy and steroid-sparing role of immunosuppressive medications such as cyclophosphamide and MMF, there is a move towards reducing exposure to oral corticosteroids and thus limiting the toxicities associated with prolonged use. Data on long-term outcomes in adults with childhood-onset INS suggest that the major impact long-term is the morbidity of prolonged systemic corticosteroid and immunosuppressant use (Trompeter et al. 1985; Fakhouri et al. 2003; Ruth et al. 2005; Noone et al. 2018). Therefore, preventing relapses and the associated oral corticosteroid use in this patient population who are at risk of frequent relapses would be clinically impactful.

To minimize steroid-related toxicity, the study design requires a rapid steroid taper for those participants who are receiving daily oral prednisone (or prednisolone equivalent) at randomization. The goal is to reach 0 mg/day by study Weeks 4–6 (and ideally no later than by Week 8) following randomization (or sooner if appropriate) and participants will continue without prednisone use through the remainder of the study.

[redacted]

[redacted] although the UPCR sample must be collected prior to initiation of corticosteroids.

The proportion of patients with sustained complete remission at 1 year as measured by UPCR at Week 52 is therefore the most informative and clinically meaningful endpoint to compare obinutuzumab versus MMF, and the Sponsor believes that this endpoint will allow the assessment of prevention of frequent relapse, and steroid-sparing effect over the 1-year treatment period.

4. STUDY DESIGN

4.1 OVERALL DESIGN

The study is a Phase III, randomized, open-label, multicenter, active comparator study to evaluate the efficacy, safety, and PK/PD of obinutuzumab versus MMF in maintaining remission in participants with childhood-onset FRNS or SDNS who have achieved complete remission upon study entry and are considered to be at high risk of relapse. The optimal goal of treatment is for maximal steroid sparing while limiting the relapse rate in this patient population.

This international study will be conducted at investigational sites throughout North America, Europe, Asia, and South America. It is expected that approximately 60 centers will participate and approximately 80 participants will enroll across all sites in a global enrollment phase. After completion of the global enrollment phase, additional participants may be enrolled at sites in China in an extended China enrollment phase to ensure a total enrollment that is sufficient to support registration in China. The global population will include all participants enrolled during the global enrollment phase (including participants enrolled at sites in China during that phase), and the China subpopulation will include all participants enrolled at sites in China (i.e., during both the global enrollment phase and the extended China enrollment phase).

Participants aged ≥2–25 years old at the time of signing informed consent must be in complete remission defined by the absence of edema, a urine protein creatinine ratio [UPCR] ≤0.2 g/g at the screening visit and have 3 consecutive daily (home-monitoring) urine dipstick readings of trace or negative for protein within the week prior to randomization. To be eligible for the study, participants must have had at least one relapse in the 6 months prior to screening after discontinuation of or while receiving oral corticosteroids and/or immunosuppressive therapy (e.g., oral cyclophosphamide, levamisole, mizoribine, MMF, or calcineurin inhibitors [CNIs]).

The study will consist of four periods: a screening period of up to 28 days in length (see Section 4.1.1), a 52-week initial open-label treatment period (see Section 4.1.2), a post-Week 52 extension period (see Section 4.1.3), and a minimum 12-month safety follow-up (SFU) period that begins at the time of study treatment completion or

discontinuation (see Section 4.1.4). A study schema is provided in Section 1.2 (see Figure 1). A Schedule of Activities and Sample Collection Schedule is provided in Table 1, Table 2, and Table 3.

4.1.1 Screening

Consenting participants will enter a screening period which should be completed within 28 days prior to randomization. The screening window may be extended by 7 days if required in case of unavoidable delay in screening assessments. Procedures at screening will include collecting a complete medical history, a full physical examination, chest X-ray (for participants aged 12 and above or as clinically indicated), ECG, and blood and urine sampling. All screening evaluations must be completed and reviewed to confirm that participants meet all eligibility criteria before randomization on Day 1, in accordance with the Schedule of Activities (see Table 1). The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. Individuals who do not meet the criteria for participation in this study (i.e., screen failure, see Section 5.4 for details) may qualify for one full re-screening opportunity (for a total of two screenings per individual) at the investigator's discretion.

During screening, participants may be receiving short term steroids if clinically indicated, up to a maximum dose of up to 1.5 mg/kg/day (maximum 40 mg/day). Participants with SDNS may be on low dose preventative therapy (e.g., less than 1 mg/kg/dose daily or alternate days). If a participant is receiving prednisone or equivalent at the screening visit, it is recommended that the dose is maintained and high enough to keep the participant in remission based on past experience until Day 16 (approximately 2 weeks after randomization) when the corticosteroid tapering should begin. Tapering off prednisone or equivalent to 0 mg/day is expected by study Weeks 4–6 (and no later than Week 8).

If a relapse event occurs during screening, the participant may be rescreened once they are in complete clinical remission again for at least one week before randomization.

4.1.1.1 Re-Testing: Laboratory Inclusion and Exclusion Criteria

If a participant does not meet the laboratory eligibility criteria at screening (see Section 5.2 and Section 5.3), the investigator may repeat the test twice within the screening period. If the participant does not meet the laboratory criteria for a third time, the participant will be considered a screen failure. It is possible to re-screen a participant. It will not be considered re-testing if blood samples have to be redrawn owing to sample handling problems, breakage, or sample integrity.

4.1.1.2 Re-Screening

Re-screening refers to repeating the entire screening process if a participant has not met all the eligibility criteria within 28 days (±7 days) of the original screening visit (Section 4.1.1). Participants are allowed to be re-screened only once. Each participant

must be re-consented before re-screening occurs. It will not be considered re-screening if blood samples have to be redrawn owing to sample handling problems, breakage, or sample integrity.

4.1.2 Study Treatment During the 52-Week Open-Label Treatment Period

Approximately 80 participants will be randomized in a 1:1 ratio to one of two open-label treatment groups: obinutuzumab (Group A) or MMF (Group B) and follow the Schedule of Activities (Table 1, Table 2, and Table 3) until the common close out date (CCOD) for the primary analysis. The primary endpoint analysis will occur when the last participant reaches the Week 52 study visit. Randomization will be stratified by the participant's disease type (FRNS vs. SDNS) and the use of immunosuppressive treatment, other than corticosteroids for INS prior to study entry (MMF/other immunosuppressive agent vs. no MMF/other immunosuppressive agent). Randomized participants will receive either an infusion of obinutuzumab 1000 mg IV on Days 1, 15, 168 (Week 24) and Day 182 (Week 26), during the initial 52-week treatment period[1] or commence or continue daily oral MMF (either tablet, capsule, or liquid formulation) on Day 1 according to Figure 1.

For those participants randomized to MMF, it may be initiated and titrated in divided doses to reach the target dose of 1200 mg/m^2/day within 4 weeks of initiation. Participants already receiving MMF prior to study entry should be titrated to the target dose of 1200 mg/m^2/day (maximum 2 g/day), given in two divided doses (600 mg/m^2 twice a day [BID]) by Day 1.

Participants who are receiving daily oral prednisone (or prednisolone equivalent) at randomization will follow the guided tapering schedule (see Table 7) to reach the goal of 0 mg/day by Week 8 following randomization (or sooner, e.g., by study Weeks 4–6 if appropriate) and continue without prednisone use through the remainder of the study.

[redacted]

- [redacted]

[redacted] or other treatments or procedures per the Investigator's best medical judgment should be delayed, if possible, for at least 6 months following the first administration of study treatment and should be considered only if a participant experiences a protocol-defined [redacted]

[1] Note: Participants with a body weight of 45 kg or more will receive the 1000 mg obinutuzumab dose. Participants with a body weight below 45 kg will receive a weight adjusted dose of 20 mg/kg for obinutuzumab infusions.

[redacted]
If participants in the MMF arm meet the criteria for rescue therapy, the patient will be considered to have met the definition of an intercurrent event and may receive [redacted]. If participants in the obinutuzumab arm meet the criteria for rescue therapy, the patient will be considered to have met the definition of an intercurrent event and may receive [redacted]. An early withdrawal visit is not required for a patient to receive rescue therapy, and patients should continue to be followed in the study per the Schedule of Activities until CCOD.

The primary endpoint of the Proportion of Participants with Sustained Complete Remission at 1 year (UPCR ≤0.2 g/g without occurrence of a relapse or other intercurrent event) will be evaluated when the last participant randomized has completed the Week 52 visit.

Participants will continue to be followed-up in their randomized treatment group through Week 52, and the treatment extension period until the CCOD and then subsequently enter SFU, as applicable (see Table 2, Table 3, and Section 4.1.4).

4.1.3 Post-Week 52 Extension Period

Post the Week 52 visit, participants will follow the Schedule of Activities according to Table 2, until the CCOD or early study withdrawal, whichever comes first. Therefore, participants who have completed their Week 52 visit will continue to be followed according to Table 2 until the last participant randomized reaches their Week 52 visit. From Week 52, MMF must be discontinued or tapered over the subsequent 3 months unless the participant experiences a protocol-defined relapse.

Participants, whether in the MMF or obinutuzumab arms, who exhibit relapse after Week 52 will be treated as per the best judgment of the investigator [redacted]

Patients who do not meet the criteria for relapse on or after Week 52 will not be eligible for [redacted] in the extension period, but should continue to be followed every 3 months at study visits until CCOD.

To be eligible for [redacted] on or after Week 52, participants must meet one of the following criteria for relapse requiring treatment:

- First-morning void UPCR >2g/g **or**

- Dipstick urinalysis (UA) ≥3+ for 3 consecutive days (home monitoring) and the most recent urine sample of the 3 day period determined to have UPCR >0.2 g/g as measured by the central laboratory **or**
- Dipstick UA protein ≥3+ on any single day with edema and urine sample determined to have UPCR >0.2 g/g as measured by the central laboratory

[redacted]

(see Table 2 and Table 3).

At the time of the primary analysis (when the last participant completes the Week 52 study visit) participants are considered to have completed the study if it has been at least 12 months since their last obinutuzumab infusion and peripheral CD19 B-cell count has returned to pre-treatment values or to within the central laboratory normal range for this patient population, whichever is lower, **or** the patient did not receive obinutuzumab.

Participants with peripheral B-cell depletion will continue to be followed in SFU every 12 weeks for 6 months, then every 6 months thereafter (see Table 5) until return of peripheral CD19 B cells to the pre-treatment value or to within the central laboratory normal range for this patient population, whichever is lower, until the end of study as described in Section 4.4.

4.1.4 Safety Follow-Up

Patients will enter the SFU schedule of activities specified in Table 4 for any of the following:

- At time of early withdrawal, or
- At the time of the CCOD, or
- If the sponsor terminates the study

The first SFU visit will be scheduled approximately 12 weeks after the last study visit in the treatment period or CCOD, whichever occurs first. No obinutuzumab infusions or MMF will be provided during SFU. Standard-of-care therapies may be provided at the investigator's discretion.

Patients who have not received obinutuzumab will be seen for only a single SFU visit, with assessments specified in SFU Visit 1.

Patients who have received obinutuzumab will be followed in SFU until such patients have fulfilled both of the following criteria:

1. Peripheral B cells have returned to pre-obinutuzumab baseline levels or to within the normal range for the population, whichever is lower.
2. The last infusion of obinutuzumab was at least 12 months ago.

Patients who have received obinutuzumab but who have not fulfilled both of the following criteria will be followed until the end of study, defined as the date when the last participant last visit (LPLV) occurs. The LPLV will occur when the last participant enrolled completes the SFU requirements, up to a maximum of 18 months from the last obinutuzumab infusion.

For example, for a patient who had received obinutuzumab 7 months before the initiation of SFU, such a patient would be seen at SFU Visit 1, approximately 12 weeks after the start of the SFU and 10 months after that patient's last infusion of obinutuzumab. Such a patient would again be seen at SFU Visit 2, approximately 12 weeks after that patient's first SFU visit. If at the SFU Visit 2, that patient's peripheral B cells had returned to pre-obinutuzumab baseline levels or to within the normal range for the population, whichever is lower, this SFU Vsit 2 would be the patient's last study visit.

At each SFU visit, the absolute CD19+ B-cell count will be measured. For participants with persistent B-cell depletion, defined as an absolute CD19+ B-cell count below the lowest pretreatment value and less than the lower limit of normal (LLN) for this population, and who have not received an additional therapy associated with reductions in peripheral B cells, SFU will continue every 6 months until any of the following occurs:

- Return of peripheral CD19+ B cells to the lowest pretreatment value or the age specific LLN for the patient population, whichever is lower
- Receipt of an additional therapy associated with reductions in peripheral B cells (e.g., belimumab, rituximab, or cyclophosphamide, or use of obinutuzumab outside the study protocol)
- The study ends as outlined in Section 4.4

4.1.5 Study Completion

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

- SFU requirements have been completed (see Section 4.1.4).
- The last study visit of treatment on or after CCOD has been completed and the investigator intends to treat the participant for nephrotic syndrome outside of the study protocol without completing the required SFU described in Section 4.1.4.
- The study ends as outlined in Section 4.4.

Upon completion of the study, the Sponsor will offer continued access to Roche investigational medicinal product (IMP; obinutuzumab) free of charge to eligible participants in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Products (see Section 6.6).

4.1.6 *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.

4.2 RATIONALE FOR STUDY DESIGN

The purpose of this open-label, randomized multicenter study is to assess the efficacy, safety, and PK/PD of obinutuzumab compared with MMF in maintaining remission in children and young adults (aged ≥2–25 years) with FRNS or SDNS.

Children and young adults with FRNS/SDNS are at risk of short-term and long-term steroid toxicity, severe infections, thromboembolic events, and acute kidney injury during relapses. The reduction of these risks is dependent on the identification of effective therapy and maintenance of clinical remission. Current standard of care remains limited to a combination of systemic corticosteroids and immunosuppressive therapies, but most available regimens confer a complete renal response in fewer than half of treated patients.

4.2.1 Rationale for Primary Endpoint

To evaluate the efficacy of obinutuzumab compared with MMF, the Sponsor proposes the clinically meaningful primary endpoint of Proportion of Participants with Sustained Complete Remission at 1 year, defined as first morning void UPCR ≤0.2 g/g at Week 52 without occurrence of a relapse or any *other* intercurrent event *as defined below*.

Participants experiencing any of the following intercurrent events occurring after Week 8 will be considered a non-responder:

- Relapse
- Any systemic corticosteroids usage for >14 days in a 30 day period

Participants experiencing any of the following intercurrent events occurring after randomization will be considered a non-responder:

- *Initiation of any rescue therapy for INS, as determined by the investigator's best medical judgement, other than systemic corticosteroids*
- *Treatment discontinuation due to lack of efficacy*
- *Death*

Intercurrent events are defined as above either because such events have the potential to impact UPCR at Week 52 or because such events would themselves represent a loss of complete remission (e.g., relapse). For the complete definition of the primary endpoint and related intercurrent events, please see Section 9.5.

Relapse will be objectively measured by the assessment of proteinuria, and the urine samples that define a relapse will be confirmed by UPCR central laboratory analysis.

Relapse will be defined by any of the following events:

- First-morning void UPCR ≥2 g/g **or**
- Dipstick UA ≥3+ for 3 consecutive days (home-monitoring) and the most recent urine sample of the 3 day period determined to have UPCR >0.2 g/g as measured by the central laboratory **or**
- Dipstick UA protein ≥3+ on any single day with edema and urine sample determined to have UPCR >0.2 g/g as measured by the central laboratory

Maintaining sustained remission in patients with FRNS/SDNS continues to be a challenge. In this patient population, where frequent relapses on a background of oral steroids and immunosuppressants are common, the goal of any new treatment option is to effectively prevent relapse and maintain patients in complete remission. Oral corticosteroids remain the mainstay of treatment for relapse. However, the extended use of oral corticosteroids is not encouraged in situations where a steroid-sparing option may be available, particularly in children who remain at risk for impaired growth and other significant side effects of steroid-related toxicity. With accumulating data on the efficacy and steroid-sparing role of immunosuppressive medications such as cyclophosphamide and MMF, there is a move towards reducing exposure to oral corticosteroids and thus limiting the toxicities associated with prolonged use. Data on long-term outcomes in adults with childhood-onset INS suggest that the major impact long-term is the morbidity of prolonged systemic corticosteroid and immunosuppressant use (Trompeter et al. 1985; Fakhouri et al. 2003; Ruth et al. 2005; Noone et al. 2018). Therefore, preventing relapses and the associated oral corticosteroid use in this patient population who are at risk of frequent relapses would be clinically impactful.

To minimize steroid-related toxicity, the study design requires a rapid steroid taper for those participants who are receiving daily oral prednisone (or prednisolone equivalent) at randomization. The goal is to reach 0 mg/day by study Weeks 4–6 (and no later than by Week 8) following randomization (or sooner if appropriate) and participants will continue without prednisone use through the remainder of the study.



The proportion of patients with sustained complete remission at 1 year as measured by UPCR at Week 52 is therefore the most informative and clinically meaningful endpoint to

compare obinutuzumab versus MMF, and the Sponsor believes that this endpoint will allow the assessment of prevention of frequent relapse, and steroid-sparing effect over the 1-year treatment period.

4.2.2 Rationale for Study Population

The proposed study population is frequently relapsing/steroid-dependent patients with childhood-onset INS who are in remission at baseline, as detailed in the inclusion criteria. Participants aged ≥2–25 years old, who have been diagnosed with childhood-onset FRNS/SDNS will be enrolled in this study to evaluate the safety and effectiveness of obinutuzumab compared to MMF in maintaining complete remission at Week 52 without experiencing a relapse, other intercurrent event or requiring additional therapy. Participants will have achieved complete remission upon study entry and are considered to be at high risk of relapse. The optimal goal of treatment is for maximal steroid sparing while limiting the relapse rate in this patient population. Complete remission upon study entry will be defined by the absence of edema, UPCR ≤0.2 g/g at screening and three consecutive daily urine dipstick readings of trace or negative for protein within the week prior to randomization. To be eligible for the study, participants must have had at least one relapse in the 6 months prior to screening, after discontinuation of oral corticosteroids or while receiving oral corticosteroids and/or other immunosuppressive therapy (e.g., oral cyclophosphamide, levamisole, mizoribine, MMF or CNIs) to prevent relapses. Maintaining sustained remission in participants with FRNS/SDNS continues to be a challenge. In this patient population where frequent relapses on a background of oral steroids and immunosuppressants are common, the goal of any new treatment option is to effectively limit oral corticosteroid exposure, prevent relapse and maintain participants in complete remission via sustained reduction in proteinuria for better long-term outcomes. Patients with primary steroid resistance (with genetic defects known to directly cause NS) and steroid-resistant NS due to secondary causes (Cil and Perwad 2018; Saleem 2019) will be excluded from the study. Despite the high unmet need in this smaller population, there are conflicting data in terms of clinical response to anti-CD20 therapy (rituximab), which suggests that these patients may not benefit from anti-CD20 therapy or respond to a lesser extent compared with the FRNS/SDNS population (Trautmann et al. 2017). Steroid-resistant patients would also likely not be in clinical remission with disease controlled at study entry, which is a key inclusion criterion.

The Sponsor also proposes to exclude patients under 2 years of age from this Study WA43380. During the first year of life, congenital (birth to age 3 months) and infantile (3–12 months) genetic disorders and congenital infections that lead to NS are much more common than are MCD and FSGS (Eddy and Symons 2003). Inherited forms of steroid-responsive and steroid-resistant NS are being increasingly recognized in children under 2 years of age. Furthermore, the possibility of inadequate immune response toward standard childhood vaccines, if treated with an anti-CD20 agent such as obinutuzumab, is a particular concern for children under 2 years of age.

4.2.3 Rationale for Control Group

Considering the proposed patient population for the study (FRNS/SDNS), obinutuzumab vs. an active comparator of MMF is considered the most appropriate study design. Children with SDNS and FRNS are at risk for short-term and long-term steroid toxicity, severe infections, thromboembolic events, and acute kidney injury. The reduction of these risks is dependent on the identification of effective therapy, and none of the current treatment options are ideal. Although prednisone/prednisolone is approved for nephrotic syndrome (NS) in some countries ("to induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus" [Deltasone USPI]), it does not have a disease-modifying effect and the proposed patient population (SDNS/FRNS) for this study is not adequately treated with this therapy.

Additionally, there are well-described toxicities associated with long-term oral corticosteroid use, and the aim of treatment in such patients is to prevent relapse with the addition of further immunosuppressant therapy to control disease activity and reduce the need for frequent administration of corticosteroids to treat relapses. Treatment guidelines in NS are targeted towards reducing overall corticosteroid exposure, and corticosteroid-sparing agents are recommended for children with FRNS/SDNS who develop steroid-related adverse effects while on oral steroids (Kidney Disease: Improving Global Outcomes Glomerular Diseases Work Group [KDIGO] 2021). For this reason, it would be ethically challenging to use prednisone alone as a comparator arm in the proposed Phase III study.

Similarly, Acthar® Gel, an adrenocorticotropic hormone, is another approved therapy for NS ("to induce a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus" [Acthar USPI]), but a recent randomized trial showed no benefit of Acthar over placebo and concluded that Acthar was ineffective at preventing disease relapses in patients with FRNS/SDNS (Wang et al. 2018).

Among children whose disease cannot be controlled well with oral corticosteroids, a number of steroid-sparing immunosuppressive agents (e.g., cyclophosphamide, levamisole, cyclosporin A, tacrolimus, MMF, and rituximab) have been shown to reduce the risk of relapse. However, high-quality head-to head data comparing these agents are limited (Mason et al. 2020).

Mycophenolate mofetil is efficacious and widely used as the steroid-sparing immunosuppressive agent of choice, particularly in steroid-dependent disease, where it has become the first-line steroid sparing treatment (i.e., the near standard of care) at many centers globally because of its favorable toxicity profile and fewer side effects compared with cyclosporine or cyclophosphamide (Ostalska-Nowicka et al. 2011; Horinouchi et al. 2018).

In summary, based upon the need for more effective steroid-sparing and less toxic therapies for SDNS and FRNS, the Sponsor hypothesizes that obinutuzumab will be more effective than MMF in maintaining remission in children who have had at least one relapse in the 6 months prior to screening, after discontinuation of oral corticosteroids or while receiving oral corticosteroids and/or other immunosuppressive therapy (e.g., oral cyclophosphamide, levamisole, mizoribine, MMF, or CNIs) to prevent relapses. To test this hypothesis, the Sponsor proposes a randomized, multicenter clinical trial to compare the effectiveness of obinutuzumab versus MMF in preventing relapse in children and young adults with SDNS and FRNS.

4.2.4 Rationale for Pharmacodynamic Biomarker Assessments

The variability in response to previous B cell-targeting therapies in childhood-onset nephrotic syndrome is incompletely understood. This variability may reflect the heterogeneity of this disease as it relates to varying degrees of B-cell involvement among participants, but it may also point to incomplete B-cell depletion. 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.

[redacted]

4.2.5 Rationale for Open-label Study Design

The Sponsor considers the randomized, open-label, active-controlled design as justified and the most feasible design for this pivotal trial to support approval. Importantly, the pre-specified primary endpoint of proportion of participants with sustained complete remission at 1 year, as measured by central laboratory confirmed proteinuria (UPCR), is by definition an objective endpoint that will limit any perceived bias due to the open-label nature of the study. Because the laboratory values in this study cannot be influenced by participants and treating physicians who are aware of treatment assignment, the open-label design should not affect efficacy outcomes. Additionally, because this will be an open-label comparison between obinutuzumab and MMF, careful measures will be taken to avoid potential bias that could compromise the integrity of the study. The same criteria for rescue therapy will be applied equally to both arms, which should help ensure uniformity in study conduct and enhance the scientific integrity of the study.
The Sponsor also has concerns with administering placebo obinutuzumab infusions in a blinded fashion to young children and believes this would be an unnecessary burden on pediatric patients. Dosing with placebo infusions could expose patients to safety events associated with administration of the infusion itself hence the open label design is in the Sponsor's opinion to be most justified.

4.3 JUSTIFICATION FOR DOSE AND SCHEDULE

The dose and dose regimen for obinutuzumab is based on experimental observation of obinutuzumab potency relative to rituximab in nonclinical experiments and in clinical studies. The proposed treatment regimen is administration as an IV infusion on

Day 1 and Day 15 with repeat infusions on Day 168 (Week 24) and Day 182 (Week 26). Participants with a body weight of 45 kg or more will receive 1000 mg, while participants with a body weight below 45 kg will receive a weight-adjusted dose of 20 mg/kg.

The pharmacokinetics of obinutuzumab have been characterized in patients with LN (Phase II Study WA29748) following single IV doses of 1000 mg on Weeks 0, 2, 24, and 26 using a population PK approach (Research Report 1101950). The covariates found to influence obinutuzumab PK parameters were [redacted] Consistent with the dependencies of PK parameters on covariates, exposure following administration of a flat dose of obinutuzumab is expected to be [redacted]. Conversely, exposure is expected to be [redacted]

The disposition characteristics for obinutuzumab in patients with childhood-onset INS are currently not known, and the impact of baseline patient characteristics ([redacted]) on exposure has not been characterized. However, PK simulations were conducted based on the model developed in LN patients to support the proposed dose and dosing regimen in the INS population. While the simulations relied on LN patient data, the demographic characteristics are considered relevant to the INS population. In Study WA29748 (NOBILTY) in adult LN, achievement of sustained peripheral B-cell depletion was associated with increased achievement of CRR, and 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.

To date, there is little clinical experience of the use of obinutuzumab in the pediatric setting, especially with multiple B-cell–depleting doses for longer-term disease control. Pharmacokinetic simulations to support the proposed dose and dosing regimen in patients with childhood-onset INS were conducted based on the model developed in patients with LN and support the proposed dose and dosing regimen in patients with childhood onset INS. The simulations indicated that the proposed dose should maintain comparable exposures (C_{max} and AUC) across the range of body weights from pediatric to adult patients. In summary, there was a good match between the predicted exposure distributions in pediatric patients with LN following the proposed pediatric dosing strategy of 20 mg/kg in patients <45 kg and a flat dose of 1000 mg in patients ≥45 kg, and administration of 1000 mg in adults.

For the planned study in childhood-onset INS, a chronic condition that may require long-term immunosuppression, the Sponsor believes that it is important to increase the

degree and duration of clinical benefit compared with MMF by maintaining sustained B-cell depletion beyond Week 26 and through at least Month 12 (Week 52). Given the primary endpoint which measures Sustain Complete Remission at 1 year, the obinutuzumab dosing regimen proposed is expected to provide sufficient pharmacodynamic effect and sustained B-cell depletion after Month 6 and through Month 12, and allow for maximal difference to be observed for SCR between the two treatment arms.

The active comparator, MMF (tablet, capsule, or liquid formulation), is dosed by body surface area in children. In order for MMF to have a comparable duration of treatment/dosing, participants randomized to MMF will receive daily oral doses through Week 52. Mycophenolate mofetil will be commenced or continued in those participants randomized to MMF therapy. Participants in the MMF arm will receive oral MMF for home administration at a standard oral daily dose of 600 mg/m^2 BID (target 1200 mg/m^2/day in divided doses, maximum 2 g/day). Starting on Day 1, MMF will be titrated by Week 4 to the target dose of 1200 mg/m^2/day and continued for 12 months until the Week 52 study visit. After Week 52, participants must discontinue or taper off MMF by Week 64.

4.4 END OF STUDY DEFINITION

Follow up of all participants per the Schedule of Activities will continue until the CCOD, when the last participant randomized has completed the Week 52 visit.

The end of this study is defined as the date when the last participant last visit (LPLV) occurs. The LPLV will occur when the last participant enrolled completes the SFU requirements, up to a maximum of 18 months from the last obinutuzumab infusion.

The LPLV is expected to occur approximately 1.5–2 years after the last participant is enrolled, assuming a 52-week treatment period and at least 12 months follow-up after the final obinutuzumab infusion at Week 26.

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

4.5 DURATION OF PARTICIPATION

The minimum duration of study participation for each individual is expected to be approximately 1.5–2 years (SFU will be a minimum of 12 months after the last obinutuzumab infusion, for all patients who have received obinutuzumab). Participants may continue to participate in the study and be followed up or receive repeat treatment according to the Schedule of Activities until the last participant recruited has participated in the study for at least 18 months. The maximum duration of study participation is estimated to be approximately 3 years, or longer if peripheral B cells remain below LLN at the clinical cut-off. In this case, participants will be required to return for SFU visits every 12 weeks for 6 months, then every 6 months thereafter until B cells return to

pre-obinutuzumab dose baseline or the central laboratory LLN of normal for the participant's population, or until the study ends as defined in Section 4.4.

5. STUDY POPULATION

Approximately 80 participants aged ≥2–25 years old with childhood-onset FRNS or SDNS in complete remission upon study entry will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Potential participants are eligible to be included in the study only if all of the following criteria apply:

- Signed Informed Consent Form
  - For participants <18 years; parent or legal guardian is able to give signed informed consent. Participant assent as appropriate if <18 years old, depending on the participant's level of understanding and per local Institutional Review Board (IRB) requirements
- Must be age ≥2–25 years old at the time of signing Informed Consent
- Ability to comply with the study protocol, in the investigator's judgment
- Diagnosis of FRNS or SDNS before the age of 18 years according to international guidelines (e.g. KDIGO 2021; *IPNA 2023 see Appendix 12*)
- Must be in complete remission defined by the absence of edema, UPCR ≤0.2 g/g at screening, and have three consecutive daily urine dipstick readings of trace or negative for protein within the week prior to randomization
- Must have had at least one relapse in the 6 months prior to screening, after discontinuation of or while receiving oral corticosteroids and/or immunosuppressive therapy (e.g., oral cyclophosphamide, levamisole, mizoribine, MMF, or CNIs) to prevent relapses.
- Patients having received cyclophosphamide in the 6 months prior to randomization must have experienced at least 1 relapse subsequent to cyclophosphamide discontinuation
- Estimated glomerular filtration rate (eGFR) within normal range for age (by modified Schwartz formula, if less than 18 years of age, or by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation if 18 years of age or older)
- For females of childbearing potential: participants who agree to remain abstinent (refrain from heterosexual intercourse) or use highly effective contraception, as defined below:
  - Females 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 the

treatment period and for 18 months after the final dose of obinutuzumab and for 6 weeks after the final dose of MMF.

- A female is considered to be of childbearing potential if she is post-menarchal, has not reached a post-menopausal 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; 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 individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation 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 males: participants who agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agree to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential, males 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. Males 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 individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation 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.

5.2 EXCLUSION CRITERIA

Potential participants are excluded from the study if any of the following criteria apply:

- Secondary nephrotic syndrome (i.e., reflux nephropathy, IgA nephropathy, lupus nephritis, etc.)
- History of steroid resistant nephrotic syndrome
- History of genetic defects known to directly cause nephrotic syndrome (i.e., *NPHS2* [podocin], *NPHS1* [nephrin], *PLCE1*, *WT1*, or other known genetic cause)

- Treatment with other immunosuppressive medications to prevent relapse, other than MMF or oral corticosteroids within 2 months prior to randomization
- Pregnancy or breastfeeding or intending to become pregnant during the study or within 18 months after the final dose of obinutuzumab, or within 6 weeks after the final dose of MMF.
- Females of childbearing potential, including those who have had a tubal ligation, must have a negative serum pregnancy test result within 28 days prior to initiation of study treatment and a negative urine pregnancy test at Day 1, prior to randomization.
- History of organ or bone marrow transplant
- Participation in another therapeutic trial within 30 days of enrollment or 5 half-lives of the investigational drug (whichever is longer)
- 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
  - Lack of peripheral venous access
  - Intolerance or contraindication to oral or IV corticosteroids
  - Intolerance or contraindication to MMF
- Patients demonstrating prior treatment failure to MMF as defined by two or more relapses in any 6-month period of time while receiving MMF for at least a 6-month duration
- Participants in the judgment of the investigator likely to require systemic corticosteroids for reasons other than idiopathic nephrotic syndrome during the study
- Receipt of any of the following excluded therapies:
  - Cyclophosphamide, levamisole, mizoribine, tacrolimus, cyclosporine, or voclosporin during the 2 months prior to screening or during screening
  - Any biologic B cell–*depleting* therapy (e.g., antiCD19, antiCD20, antiCD22, such as, but not limited to, rituximab, ocrelizumab, or ofatumumab [redacted].
  - Any biologic therapy (other than *antiCD19, antiCD20, antiCD22*) such as, but not limited to *belimumab, daratumumab,* 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

- Active infection of any kind (excluding fungal infection of nail beds) or any major episode of infection requiring hospitalization or treatment with IV antiinfective medications within 4 weeks prior to screening, or completion of oral antiinfectives within 2 weeks prior to randomization
  - Entry into this study may be reconsidered once the infection has fully resolved
- Evidence of active tuberculosis (TB) infection
  - Testing for latent TB will be performed at screening if required by local regulations or in accordance with local clinical practice.
  - Latent TB after completion of appropriate treatment per local clinical guidelines is not exclusionary
- History of or currently active primary or secondary immunodeficiency, including known history of HIV infection and other severe Immunodeficiency blood disorders.
  - For participants with unknown HIV status, HIV testing may be performed at screening if required by local regulations
- History of serious recurrent or chronic infection
- History of progressive multifocal leukoencephalopathy
- History of or current cancer, including solid tumors, hematological malignancies, and carcinoma in situ (except basal cell carcinoma and squamous cell carcinoma of the skin that have been excised and cured) within the past 5 years
- Major surgery requiring hospitalization during the 4 weeks prior to screening or during screening
- High risk for clinically significant bleeding or any condition requiring plasmapheresis, intravenous immunoglobulin, or acute blood product transfusions
- Evidence of any significant or uncontrolled concomitant disease that, in the investigator's judgment, would preclude participant's participation, including but not limited to nervous system, respiratory, cardiac, hepatic, endocrine, malignant, or gastrointestinal disorders
- Currently active alcohol or drug abuse or history of alcohol or drug abuse
- Any of the following laboratory parameters at screening:
  - AST or ALT $>2.5\times$ upper limit of normal (ULN) (for age and sex) that cannot be attributed to underlying nephrotic syndrome
  - Amylase or lipase $>2\times$ ULN
  - Absolute neutrophil count $<1.5\times10^3/\mu L$
  - Hemoglobin <8 g/dL
  - Platelet count $<110{,}000/\mu L$ for participants below age 12 and $50{,}000/\mu L$ for patients age 12 or above
  - Positive hepatitis B surface antigen
  - Positive hepatitis B core antibody

- Positive hepatitis C antibody
- Positive serum human chorionic gonadotropin measured at screening

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

This study has no meal or dietary restrictions.

5.3.2 Caffeine, Alcohol, and Tobacco

This study has no caffeine, alcohol, or tobacco restrictions.

Participants with current active alcohol or drug abuse or history of alcohol or drug abuse are excluded from the study (see Section 5.2).

5.3.3 Activity

This study has no activity restrictions.

5.3.4 Contraception Requirements

During the study, participants must use contraception or take other precautions as described in Section 5.1.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimum set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from health authorities. Minimum information includes demography, reason for screen failure eligibility criteria, and any serious adverse event.

Individuals who do not meet the criteria for participation in this study (screen failures) may qualify for one full re-screening opportunity (for a total of two screenings per individual) at the investigator's discretion (see Section 4.1.1.2).

Individuals must re-sign the consent form prior to re-screening. The investigator will record reasons for screen failure in the screening log (see Section 8).

6. STUDY TREATMENT(S) AND CONCOMITANT THERAPY

Study treatment is defined as any investigational treatment, marketed product, placebo, or medical device intended to be administered to a study participant according to the study protocol.

The IMPs for this study are obinutuzumab and MMF. Locally sourced prednisone, pre-medications used prior to infusions of obinutuzumab and standard-of-care rescue

medications or other treatments or procedures initiated for INS per investigator discretion, are considered non-investigational medicinal products *(NIMP). Appendix 13 identifies all IMPs, auxiliary medicinal products (AxMP),and NIMPs for this study.*

6.1 STUDY TREATMENTS ADMINISTERED

Table 6 provides a description of assigned study treatments for this study.

Table 6 Study Treatment Description

	Obinutuzumab	MMF	Prednisone	Methylprednisolone	[redacted]	Diphenhydramine Hydrochloride
Use	Experimental	*Active Comparator*	Background treatment	Premedication		Premedication
Drug form	Liquid concentrate	Tablet/capsule/liquid formulation [a]	Tablet	Liquid concentrate		Tablet
Dosage Level(s)	1000 mg (or 20 mg/kg if < 45 kg)	1200 mg/m2/day (maximum 2000 mg/day) in two divided doses.	Standardized tapering schedule through Week 8	80mg (or 1.5 mg/kg if ≤45 kg)		0.5–1 mg/kg (rounded to the nearest available pill formulation, maximum dose 50 mg)
Formulations	Refer to pharmacy manual and the Obinutuzumab Immunology Investigator's Brochure	Refer to *pharmacy manual and* local prescribing information.	Refer to local prescribing information.	Refer to local prescribing information.		Refer to local prescribing information.
Packaging	50-mL glass vial	500 mg tablet bottle or blister pack or 250 mg capsule [a] bottle or blister pack or wallet or 1 g/5 ml (200 mg/ml) bottled liquid formulation	As described in local prescribing information	As described in local prescribing information		As described in local prescribing information
Labeling			Per local requirements			

IMP = investigational medicinal product; MMF = mycophenolate mofetil; NIMP = non-investigational medicinal product; PO = orally.

Table 6 Study Treatment Description (cont.)

	Obinutuzumab	MMF	Prednisone	Methylprednisolone	[redacted]	Diphenhydramine Hydrochloride
Route of administration	IV	PO	PO	IV		PO or IV
Source	Sponsor	Sponsor	Local site/per local regulations	Local site/per local regulations		Local site/per local regulations

IMP=investigational medicinal product; MMF=mycophenolate mofetil; NIMP=non-investigational medicinal product; PO=orally.

[a] 250mg capsule formulation to be used in China only.as liquid formulation and 500mg tablet are not available for use in China.

The treatment regimens are summarized in Section 4.1.

Guidelines for dose modification and treatment interruption or discontinuation for participants who experience adverse events are provided in Appendix 3.

6.1.1 Obinutuzumab

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

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. Administration of obinutuzumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 7.

Obinutuzumab infusions will be administered per the instructions outlined in Appendix 10 and additional guidance for study drug administration is found in Section 6.1 above.

Guidelines for medical management of infusion related reactions (IRRs) are provided in the Appendix 3.

Randomized Group A: If participants are receiving MMF during screening, this must be discontinued by Day 1 randomization. Participants randomized to Group A will receive obinutuzumab 1000 mg (or 20 mg/kg for participants <45 kg) to be administered by IV infusion on Days 1, 15, 168 (Week 24), and 182 (Week 26). See Appendix 10 for complete details on obinutuzumab and MMF administration.

The dose of obinutuzumab will be based on the participant's baseline weight (measured ≤14 days prior to initiation of study treatment) and will remain the same throughout the study unless the participant's weight changes by >10% relative to the weight recorded at the time of the previous dose calculation.

Infusions can be given in a day care or inpatient setting. It is acceptable to hospitalize a participant as per local clinical practice.

In order to reduce the frequency and severity of infusion-related reactions, the following pre-medications will be administered prior to obinutuzumab infusions:

- Methylprednisolone: 80 mg (or 1.5 mg/kg if ≤45 kg) administered by slow IV infusion
- [redacted]

- Diphenhydramine hydrochloride: 0.5–1 mg/kg (rounded to the nearest available pill formulation, maximum dose 50 mg PO or intravenous equivalent, or equivalent dose of a similar agent by mouth or in accordance with local approved labeling)

The administration of all pre-medications must be completed between 30 and 60 minutes prior to the start of each obinutuzumab infusion.

- Note: If applicable, participants should be cautioned not to operate vehicles or hazardous machinery until their response to diphenhydramine (or similar antihistamine) has been determined

6.1.2 Mycophenolate Mofetil

Randomized Group B: Participants in the MMF arm will receive oral mycophenolate mofetil via home administration from the baseline visit (Day 1) onward. MMF will be titrated by Week 4 to a target dose of 1200 mg/m^2/day (maximum 2 g/day), given in two divided doses (600 mg/m^2 BID). See Appendix A10–2 for complete details on MMF dosing.

- The body surface area (BSA)-based target dose may be rounded to the nearest 500-mg dose.
- MMF should continue to be administered daily for at least 12 months until the Week 52 study visit, after which time it must be discontinued or tapered over the subsequent 3 months by Week 64.

If participants are receiving MMF during screening they should continue to receive their prescribed daily doses up to Day 1 when the study treatment will commence. Participants randomized to Group B will commence oral MMF from the baseline visit (Day 1) visit.

On/after Week 52, participants must discontinue or taper off MMF by Week 64 unless the participant experiences a protocol-defined relapse. Patients who experience a protocol-defined relapse after Week 52 should be treated according to the investigator's best clinical judgment (see Section 6.1.4). Mycophenolate mofetil will be dispensed by the clinical or research pharmacy at the site. MMF is available as tablets (500 mg) and as a powder for oral suspension containing 200 mg/ml upon reconstitution. In China, MMF is available as 250 mg capsules only. Dosing will be based on BSA (600 mg/m^2), with a maximum dose of 2 g/day outside of a relapse event. For a relapse event, the maximum dosage of MMF will be 2.5 g/day or 1200 mg/m^2/day, whichever is lower. The decision of whether a participant will receive a tablet (or capsule, if applicable) or liquid will be based on whether the parent/investigator believes the participant can swallow the tablets (or capsules). If the participant is unable to swallow tablets (or capsules), then the liquid preparation will be prescribed, per local labeling and availability, as applicable.

Dosing of the liquid preparation will be *rounded down* to the nearest *50* mg (*0.25* ml) *of* the calculated dose (e.g., calculated=235 mg; prescribed *200* mg).

The BSA-based target dose may be rounded to the nearest dose given the available tablet size (500 mg) or capsule size (250 mg in China), but this should not exceed the calculated dose amount.

- Adjustments to MMF dosing will only be permitted because of intolerance and adverse events. Participants should notify the site/investigator as soon as possible if they are unable to tolerate MMF at the dose prescribed.
- MMF should be taken at approximately the same times each day, ideally on an empty stomach (1 hour before or 2 hours after meals) in the morning and evening.
- MMF tablets or capsules should be swallowed whole with a glass of water and should not be chewed, cut, or crushed. As such, morning and evening doses of MMF may differ: for example, a participant requiring 1.5 g daily may take 1000 mg every morning and 500 mg every evening. Whether the higher dose is taken in the morning or evening is per investigator (and participant) discretion but should be consistent on a daily basis.
- MMF will be provided to the participant for home administration. To assess participant compliance with self-administration of MMF, participants (or parents/legal guardian, as applicable) will be required to record the date they took each dose in a medication diary; missed doses will also be recorded.
- Participants (or parents/legal guardian, as applicable) will be instructed to bring all unused study medication and their medication diaries at specified study visits for assessments of compliance.
- MMF should be maintained at the target dose throughout the study until Week 52 After Week 52, MMF must be discontinued or tapered over the subsequent 3 months by Week 64.

6.1.3 Oral Corticosteroid Treatment

During screening, participants may be receiving short term oral corticosteroids if clinically indicated, up to 1.5 mg/kg/day (maximum 40 mg/day). Participants with SDNS may be on low dose preventative therapy (e.g., less than 1 mg/kg/dosed daily or alternate days). If a participant is receiving prednisone or equivalent at the screening visit , it is recommended that the dose is maintained and high enough to keep the participant in remission based on past experience until Day 16 (approximately 2 weeks after randomization) when the corticosteroid tapering should begin according Table 7.

During the study period, participants who are receiving daily oral prednisone (or prednisolone equivalent) at randomization will follow the guided tapering schedule (see Table 7) to reach the goal of 0 mg/day by study Weeks 4–6 (and no later than Week 8) following randomization and continue without prednisone use through Week 52. The decision to taper the corticosteroid dose can be affected by physician preferences, participant tolerability, and local practices, among other considerations. The [redacted] Prednisone (or equivalent) will be sourced locally.

Oral prednisone should be withheld in the obinutuzumab arm on days (Day 1, Day 15, Week 24, and Week 26 infusion visits) when pre-infusion methylprednisolone is given.

On Day 2, all participants may receive oral prednisone up to 1.5 mg/kg/day (maximum 40 mg/day) and remain on a stable dose until the Week 2 visit. Beginning on Day 15, prednisone will be tapered, as clinically indicated, to achieve a target prednisone (or equivalent) dose of 0 mg/day by study Weeks 4–6 (and ideally no later than Week 8) according to the guided steroid taper below.

If clinically appropriate, prednisone will be maintained at 0 mg/day from Week 8 (or from the time oral corticosteroids are initially tapered to 0mg/day if before Week 8) through the remainder of the study.

Usage of systemic corticosteroids after week 8 for *more than* 14 days in a 30 day period, or *failure to complete protocol-defined steroid taper by week 8*, will count toward meeting the definition of an intercurrent event for the purposes of study outcomes. Initial steroid taper will be considered to be complete before week 8 if a patient has not required systemic corticosteroids for at least 7 days after taper.

For patients who require an increase in systemic corticosteroids before Week 8, but subsequently complete the taper by Week 8 and do not require steroids through Week 52, criteria for an intercurrent event would not be considered met.

For patients who complete the steroid taper by Week 8 but receive additional steroids after Week 8 but do not meet the definition of "systemic corticosteroid usage for > 14 days in a 30 day period," these patients will not be considered as non-responders or to have an event because they do not meet the definition and will be followed as normal to Week 52.

Patients who do not complete the protocol-defined steroid taper (i.e., still receiving systemic corticosteroid after Week 8 for *more than* 14 days in a 30-day period) will be treated as non-responders for binary outcomes and an event for the overall RFS.

Of note, some patients (e.g., patients with SDNS) may not adhere to the 8 week steroid taper and may need additional time for tapering to occur. In cases where investigators extend the tapering period for individual patients beyond Week 8, this is permitted as long as "systemic corticosteroid usage for > 14 days in a 30 day period" does not occur after Week 8, as this would be an intercurrent event and the patient would be treated as a non-responder for the binary outcome and overall RFS

See Table 7 for steroid-tapering guidance.

Table 7 Oral Corticosteroid Tapering Guidelines

Study Date	Dose of Oral Prednisone or Equivalent (mg/day) [a]			
Days 2–14	15.0	20.0	30.0	40.0
Day 16 [b]	5.0	10.0	20.0	30.0
Week 4	0.0	5.0	15.0	20.0
Week 6	0	0	10.0	10.0
Week 8—End of study	0	0	0	0

Oral corticosteroid dose reductions are suggested guidance and may be recommended to occur on or around the specified timepoints if clinically appropriate. The stepwise tapering of oral corticosteroids, for those participants receiving them at baseline, should be performed at the discretion of the investigator. All prednisone (or equivalent) doses and adjustments should be recorded on the appropriate electronic Case Report Form.

[a] For those participants receiving oral prednisone, this may continue at a dose of up to 1.5 mg/kg/day (maximum 40 mg/day) on Day 2. Starting doses should be rounded to the nearest milligram 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. *Alternate day dosing of steroids that is equivalent to the daily steroid doses listed are also permitted (e.g. 60 mg of prednisone given on alternating days is equivalent to 30 mg per day).*

[b] Steroid taper attempt should begin on Day 16 (oral prednisone should be withheld on obinutuzumab infusion days).

[redacted]

- [redacted]

[redacted]

- First-morning void UPCR >2 g/g or
- Dipstick UA ≥3+ for 3 consecutive days (home-monitoring) and the most recent urine sample in the 3 day period determined to have UPCR >0.2 g/g as measured by the central laboratory or
- Dipstick UA protein ≥3+ on any single day with edema and urine sample determined to have UPCR >0.2 g/g as measured by the central laboratory

[redacted] However, the urine collection for UPCR central measurement should be collected before the initiation of relapse therapy. The site must review the UPCR result expeditiously after receipt from the central laboratory. [redacted]

[redacted]

In the case of relapse during the protocol defined corticosteroid taper (Table 7), a step up or increase in oral prednisone or equivalent may be appropriate per clinical judgement.

6.1.4 Rescue Therapy

For patients who experience a relapse whist in the study, the use of rescue therapy (e.g., local standard of care medications, other treatment or procedure for INS) is permitted at the investigator's discretion, and patients may be treated according to the investigator's best medical judgment.

Relapse is defined by any of the following events:

- First-morning void UPCR≥2 g/g, or
- Dipstick UA≥3+for 3 consecutive days (home-monitoring) and the most recent urine sample in the 3 day period determined to have UPCR>0.2 g/g as measured by the central laboratory, or
- Dipstick UA protein≥3+on any single day with edema and urine sample determined to have UPCR>0.2 g/g as measured by the central laboratory

[redacted]

- [redacted]

[redacted] or other treatment or procedure per the Investigator's best medical judgment should be delayed in both treatment arms, if possible, for at least 6 months following the first administration of study treatment. Rescue therapy may be considered if a participant experiences a protocol-defined relapse after completion of the guided steroid taper and with documented central-lab confirmed UPCR >0.2 g/g.

For participants whom the Investigator has determined that rescue therapy is clinically appropriate, the Investigator must receive verification that the study participant has met protocol-defined criteria for relapse, thus requiring rescue therapy before administration

of any such rescue therapy, or before [redacted], as applicable.

The date and time of rescue medication administration, as well as the name and dosage regimen of the rescue medication, must be recorded in the electronic Case Report Form (eCRF).

[redacted]

[redacted]

An early withdrawal visit is not required for a patient to receive rescue therapy, and patients should continue to be followed in the study per the Schedule of Activities until CCOD. Participants receiving more than 14 days of corticosteroids in a 30 day period after Week 8 will be considered to have had an intercurrent event.

Participants who receive rescue with [redacted].

In some cases of worsening or severely active disease, the investigator may conclude that the participant has failed the randomized treatment regimen and requires rescue therapy [redacted]. Because rescue therapies may affect subsequent efficacy assessments, participants receiving any of the following or additional rescue therapies for INS, [redacted], will be considered to have had an intercurrent event:

- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

The detailed specification and handling of intercurrent events can be found in Section 9.

Participants who receive rescue therapy for relapse with any immunosuppressive agent [redacted] (described above) prior to Week 52, will discontinue their randomized obinutuzumab or MMF study medication and will not be eligible for the extension period after Week 52. These participants will continue to be followed according to the study Schedule of Activities through Week 52 and in SFU for at least 12 months from the last dose of obinutuzumab (see Section 4.1.4).

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel e.g., pharmacist, or mobile nurse) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that participants are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP.
The study site will acknowledge receipt of IMPs supplied by the Sponsor using an interactive voice or web-based response system (IxRS) or by returning the appropriate documentation form to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs.
All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only participants enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

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 accountability log.

Refer to the pharmacy manual and/or the obinutuzumab Investigator's Brochure and MMF local prescribing information for information on IMP preparation, storage, handling, and accountability.

6.3 TREATMENT ASSIGNMENT

This is a randomized, open-label study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a participant, the study site will obtain the participant's identification number and treatment assignment from an IxRS.

Participants will be randomly assigned to one of two treatment arms: obinutuzumab or MMF. Randomization will occur in a 1:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm.

6.4 STUDY TREATMENT COMPLIANCE

When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded on the eCRF. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

When participants self-administer study treatment at home, compliance with study treatment will be assessed via Investigator review of the medication diaries periodically at study visits.

6.5 DOSE MODIFICATION

Study dose modification of the randomized treatment is generally not permitted during the study, with the exceptions noted below.

The rate of obinutuzumab infusion may be adjusted in the event of an IRR.
See Table A10-3.

If a participant experiences an IRR that requires interruption of the infusion and the investigator determines to permanently discontinue obinutuzumab infusions, the participant should continue to be followed in the study for safety. Participants who experience a Grade 4 (life-threatening) event during an infusion of obinutuzumab should

have their infusion stopped. Additional infusions of obinutuzumab should not be given. Guidelines for obinutuzumab dosage modification and treatment interruption or discontinuation are provided in Appendix 10.

If a participant experiences a new infection between the Day 1 and Day 15 infusions or between the Day 168 and Day 182 infusions (or between any two infusions in subsequent courses), the second infusion should be delayed (up to a maximum of 28 days from the scheduled first infusion date) until the infection has completely resolved and treatment with any antibiotic medications have been completed. This will not affect the participant's eligibility to receive further infusions of obinutuzumab as required.

Refer to Appendix A10–2 or prescribing information for MMF dose modification guidance.

During the initial treatment period until Week 52, the MMF dose should remain as stable as possible. If reductions in dose are necessary because of tolerability, decreases will be allowed in 500-mg decrements and must be recorded on the appropriate eCRF (see Section A3–3.1). If neutropenia develops (ANC $< 1.3 \times 10^9$/L), dosing with MMF should be interrupted or the dose should be reduced, as described in Appendix 10 or in the prescribing information. The target MMF dosage for the protocol is 1200 mg/m^2/day *(maximum* 2.0 g/day).

In the event that the participant develops a medically significant National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade 3 (severe) or Grade 4 (life-threatening) infection, no further doses of obinutuzumab or MMF treatment should be provided until the infection has resolved.

6.6 CONTINUED ACCESS TO STUDY TREATMENT AFTER THE END OF THE STUDY

The Sponsor will offer continued access to Roche IMPs (obinutuzumab and MMF) free of charge to eligible participants in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A participant will be eligible to receive Roche IMPs (obinutuzumab and MMF) after completing the study (including required SFU) if all of the following conditions are met:

- The participant 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 participant
- The participant and his or her doctor comply with and satisfy any country-specific legal or local regulatory requirements that apply to them

A participant will not be eligible to receive Roche IMPs (obinutuzumab and MMF) after completing the study if any of the following conditions are met:

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

Participants may be eligible to receive obinutuzumab and MMF as part of the post-Week 52 treatment extension period, as described in Section 4.1.3 .

6.7 TREATMENT OF OVERDOSE

An overdose is the administration of a drug in a quantity that is higher than the assigned dose. There is no known antidote for treating an overdose. Cases of overdose, along with any associated adverse events, should be reported as described in Appendix 2.

In the event of an overdose, the investigator should take the following steps:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any adverse event or serious adverse event and laboratory abnormalities until MMF and/or obinutuzumab can no longer be detected systemically (per product label).

Decisions regarding dose interruptions or modifications of study treatments will be made by the investigator in consultation with the Medical Monitor on the basis of clinical evaluation of the participant.

6.8 CONCOMITANT THERAPY

Any prescription drugs, vaccine, and other medications, including over-the-counter or prescription medicines, vitamins, and/or nutritional supplements, used by a participant in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment to the study completion/discontinuation visit must be recorded on the Concomitant Medications electronic Case Report Form (eCRF) along with the following information:

- Reason for use
- Dates of administration, including start and end dates

- Dosage information, including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

[redacted]

Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Medical Monitor.

6.8.1 Other Permitted Therapy

In general, investigators may manage a participant's care (including preexisting conditions) through use of supportive therapies, as clinically indicated and per local standard practice, with the exception of prohibited therapies defined in Section 6.8.3 and taking into account cautionary therapies defined in Section 6.8.2. Participants who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

6.8.2 Cautionary Therapy

6.8.2.1 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 participant's vaccination record and the need for immunization be carefully evaluated prior to study entry.
For participants who are likely to require immunization in the foreseeable future, such as participants planning to travel to countries where specific immunization is required or participants requiring a vaccination/booster for their professional activity, any required vaccination/booster must be given at least 28 days prior to randomization and the first administration of study medication. Review of a participant'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.

COVID-19 vaccination is allowed before or during the study. It is strongly recommended that the COVID-19 vaccinations should be taken at least 28 days prior to randomization because COVID-19 vaccination may not be as effective while taking immunosuppressants, including therapies that deplete B cells like obinutuzumab. Participants should plan the timing of vaccinations with their study doctor. Where applicable, it is recommended that local laws and guidelines should be followed with regards to COVID-19 vaccination for children and young adults.

The safety and efficacy of immunization with a live or attenuated vaccine in B cell-depleted participants is 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 prohibited for 28 days prior to randomization, during participation in the study, and whilst the participant's peripheral B cells are depleted below the central laboratory lower limit of normal.

Vaccines that do not contain live organisms (e.g., some forms of influenza, Pneumovax®, tetanus, coronavirus) are not prohibited; however, response rates to non live vaccines received during periods of peripheral B-cell depletion may be reduced or suppressed.

Participants who are eligible for yearly influenza vaccine or who require other non-live booster vaccinations can receive vaccination with killed or toxoid vaccines in accordance with normal clinical practice.

6.8.2.2 Herbal Therapies

Concomitant use of herbal or homeopathic therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown.

6.8.3 Prohibited Therapy

6.8.3.1 Prohibited Concomitant Therapies through Week 52

Through Week 52, use of the following concomitant therapies is prohibited:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
  - [redacted]

–
–
- [redacted]
- [redacted]

[redacted]

[redacted]

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

Study and site closure is described in Appendix 1.

7.1 DISCONTINUATION OF STUDY TREATMENT

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study treatment. If study treatment is definitively discontinued, the participant will remain in the study for additional assessments. See Schedule of Activities (see Section 1.3) for data to be collected at the time of discontinuation of study treatment and for any further follow-up evaluations that need to be completed.

Participants must permanently discontinue their randomized study treatment if any of the following criteria are met:

- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant
- Pregnancy
- Any event that meets stopping/permanent discontinuation criteria as defined in Appendix 3

- *Life-threatening (grade 4)* IRR or recurrence of *severe (grade 3)* IRR upon re-challenge; *for children below 12 years of age, therapy should be discontinued if an IRR is severe and deemed clinically serious (according to protocol-defined criteria for serious adverse events) or in the setting of escalation from moderate to severe IRR upon rechallenge*
- *Severe or life-threatening neutropenia (ANC below 1.0 x10³ cells/μL) that does not resolve to mild or moderate neutropenia (ANC higher than 1.5 x10³ cells/μL) within 8 weeks is a treatment-discontinuation criterion*
- *For participants <12 years of age, platelet counts that remain below 110,000 cells/μL for longer than 8 weeks is a treatment discontinuation criterion. For participants ≥ 12 years of age, platelet counts that remain below 50,000/μL for longer than 8 weeks is a treatment discontinuation criterion.*
- Progressive multifocal leukoencephalopathy
- Receipt of any rescue therapy for INS as defined in Section 6.8.1

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Participants who discontinue study treatment prematurely will not be replaced. Any participant who discontinues treatment should continue to undergo protocol mandated visits through Week 52.

Refer to the Schedule of Activities in Section 1.3 (see Table 3) for details on follow-up assessments to be performed for participants who permanently discontinue study treatment. If a participant requests to be withdrawn from treatment or follow-up assessments, this request must be documented in the source documents and signed by the investigator.

7.1.1 Liver Chemistry Stopping Criteria

Discontinuation of study treatment is required by the investigator when a study participant meets abnormal liver tests as outlined in Appendix A2–7.7, or if the investigator believes that it is in best interest of the participant when abnormal liver chemistries not meeting protocol-specified stopping rules.

7.2 PARTICIPANT DISCONTINUATION OR WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his or her own request or may be discontinued at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a participant requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the Schedule of Activities (see Section 1.3). Refer to the

Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued both from the study treatment and from the study at that time.

If a participant withdraws consent from the study, the Sponsor may retain and continue to use any data collected before withdrawal of consent. Samples collected prior to withdrawal may be analyzed, unless the participant specifically requests that the samples be destroyed (as documented in the source documents) 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.

7.3 PARTICIPANTS LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule. If the participant is unable or unwilling to comply with study visits, site personnel should assess reasons the participant is unable or unwilling to return to the clinic and determine if there are ways to support participant participation.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he or she will be considered lost to follow-up and will be withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Written informed consent for participation in the study must be obtained from a parent or guardian before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled individuals and for individuals who are not subsequently enrolled will be maintained at the study site. A copy of the signed form must be given to the participant's legal guardian.

Before conducting any study-related procedures, a signed Assent Form from participants *between 2 and 18 years of age may* be obtained, *as appropriate, depending on the participant's level of understanding and per local Institutional Review Board (IRB)*

requirements. Participants who enroll in the study who are less than 18 years old, but who will turn 18 during the study or are no longer a minor as defined in national law, will be asked to re-sign the main consent form to continue participation in the study. The investigator must maintain the original, signed consent form. A copy of the signed Assent Form must be given to the participant's legal guardian.

Study procedures and their timing are summarized in the Schedule of Activities (see Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

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

Medical history and baseline conditions, 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. Any prescription drugs, vaccine, and other medications (including over-the-counter or prescription medicines, vitamins, and/or nutritional supplements) used by the participant within 7 days prior to initiation of study treatment will be recorded at baseline. Demographic data, including age, sex, and self-reported race/ethnicity, will also be recorded. 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.

Participants will be closely monitored for safety throughout the study. Participants should be assessed for toxicity prior to each dose; treatment will be administered only if the clinical assessment and local laboratory test values are acceptable. Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

At applicable sites, certain study assessments may be performed by an MN (mobile nursing) professional at the participant's home or another suitable location, such as local clinic to improve access and convenience for participants participating in the study. The Sponsor will select a health-care 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 participant and the participant gives written informed consent to participate in MN visits, the MN network will communicate with the participant and the participant's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional.

MN visits may be scheduled for visits without obinutuzumab infusions or investigator efficacy evaluations and at visits in which no planned treatment decision is scheduled. The following visits are not eligible for MN visits: Screening, Days 1, 15, 168 (Week 24), 182 (Week 26), 364 (Week 52), early study discontinuation, SFU visits, unscheduled visits, and obinutuzumab infusion administration visits in the treatment extension period after Week 52.

8.1 EFFICACY ASSESSMENTS

8.1.1.1 Response Evaluation

Objective proteinuria response will be determined by the central laboratory UPCR at specified timepoints according to the Schedule of Activities. Assessments should be performed by the same individual, if possible, to ensure internal consistency across visits.

Endpoints (Sustained complete remission, relapse-free survival) will be calculated programmatically by the Sponsor on the basis of investigator assessment/central laboratory confirmation of relapse at each specified timepoint.

8.1.2 Clinical Outcome Assessments

Participant-reported outcome (PRO) and clinician-reported outcome (ClinRO) instruments will be completed to assess the treatment benefit of obinutuzumab.

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

8.1.2.1 Pediatric Quality of Life Inventory—4.0 Generic Core Scale

The Pediatric Quality of Life Inventory 4.0 Generic Core Scale (Appendix A5–2) is a 23-item, self-reported measure used to assess health related quality of life, over a recall of either one month (standard version) or 7 days (acute version; Varni et al. 1999; Varni et al. 2001). Items are rated on a 5-point Likert scale ranging from 0 (never a problem) to 4 (almost always a problem). Once completed, 0–4 items are reverse scored and linearly transformed to a 0–100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0, with higher scores indicating better health-related quality of life. The scale can be scored by domain, summary score and total scale score. Four core domains exist, which include Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items), and School Functioning (5 items). The summary scores include a Psychosocial Health Summary (mean of the emotional, social, and school domain) and a Physical Health Summary score (the same as the Physical Functioning domain score). A total scale score can also be calculated by taking the mean of all items answered.

Different age--appropriate versions of the measure exist, consisting of a child report (age 8–12,), teen report (age 13–18), young adult report (age 18–25) and adult report (age 26+). A parent report (ObsRO) also exists for all age versions and for individuals younger than 8 years old. The measure takes approximately 5–7 minutes to complete.

8.1.2.2 Pediatric Quality of Life Inventory - Multidimensional Fatigue Scale

The PedsQoL–Multidimensional Fatigue Scale (Appendix A5–3) is an 18-item, self-reported measure designed as a generic symptom-specific instrument to assess fatigue in patients with acute or chronic health conditions (Varni et al. 2002). There is a standard version with a one--month recall period or an acute version with a 7-day recall period. The measure assesses three components of fatigue: General Fatigue (6 items), Sleep/Rest Fatigue (6 items), and Cognitive Fatigue (6 items). Items are based on 3- and 5-point Likert response formats and transformed to 0–100 total score where a higher score indicates less fatigue. *The* scoring of individual domains is also possible. The measure takes approximately 5–7 minutes to complete.

8.1.2.3 *Supplemental Questionnaire for Fatigue and Physical Functioning*

The Supplemental Questionnaire for Fatigue and Physical Functioning will only be administered at Week 52. There are two versions of the questionnaire: a patient self-report version (Appendix A5–8) and a parent/caregiver version (Appendix A5–9). This questionnaire asks the patient to report their degree of change in fatigue and physical functioning, and if these changes are meaningful improvements. The results of these assessments will be used as an "anchoring endpoint" to derive MCIDs for the PedsQol instruments listed above (Sections 8.1.2.1 and 8.1.2.2).

8.1.2.4 Cure Glomerulonephropathy Edema Scale

The Cure Glomerulonephropathy (CureGN) Edema Scale (Appendix A5–4) can be self-administered or administered by a parent or caregiver. It was developed by the CureGN Consortium to be included in their ongoing study collaborations (e.g., Canetta et al. 2019). The version being used in the current study has a one-month recall period. Participants are asked to report the location of edema they have experienced over the last month from eight different body areas (whole body, face, hands, arms, abdomen, genitalia, legs, feet) and rate its severity on a 6-point Likert scale (0="absent"; 5="worst imaginable"). Several calculations are possible using this scale, including estimates of: (1) any edema; (2) location of edema; (3) worst reported edema severity; and (4) total edema severity summed across all eight body areas.

8.1.2.5 Subject Global Assessment of Disease Activity

The Subject's Global Assessment of Disease Activity (SGA) (Appendices A5–5 and A5–6) is the participant's overall assessment of his or her current disease activity. It is measured on a 100-mm horizontal visual analogue scale (VAS). The left-hand extreme of the line is described as "none" (symptom-free) and the right-hand extreme as "severe."

Clinician-reported outcome data will be collected through use of the instruments described below.

8.1.2.6 Physician's Global Assessment of Disease Activity

The Physician's Global Assessment of Disease Activity (PGA) (Appendix A5–7) is the physician's overall assessment of the participant's current disease activity. It is measured on a 100-mm horizontal VAS. The left-hand extreme of the line is described as "none" (symptom-free) and the right-hand extreme as "severe."

8.2 SAFETY ASSESSMENTS

8.2.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments 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.

A brief physical examination will include, at a minimum symptom-directed physical examinations. Investigators should pay special attention to clinical signs related to previous serious illnesses. Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities beyond expected variation or normal age-related changes should be recorded as adverse events on the Adverse Event eCRF. Brief physical examinations may be performed by an MN professional.

8.2.2 Vital Signs

Temperature, pulse rate, respiratory rate, and systolic and diastolic blood pressure will be assessed at the times indicated in the Schedule of Activities. Blood pressure and pulse measurements should be preceded by a few minutes of rest for the participant in a quiet seated setting without distractions.

Vital signs should be taken before blood collection for laboratory tests and should consist of one pulse and three blood pressure measurements (three consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the three blood pressure readings will be recorded on 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. Vital sign measurement may be performed by an MN professional.

8.2.3 Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the Schedule of Activities (see Section 1.3) using an ECG machine that automatically calculates the heart rate and

measures PR interval, QRS interval. See Appendix 3 for withdrawal criteria and any additional readings that may be necessary.

Lead placement should be as consistent as possible. The ECG recordings must be performed after the participant 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 reports. Paper copies of ECG tracings will be kept as part of the participant's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular post-dose timepoint the mean QT interval corrected through use of Fridericia's formula (QTcF) is >500 ms and/or >60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard of care treatment may be instituted at the investigator's discretion. If a PK sample is not scheduled for that timepoint, a PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Appendix 3. The investigator should also evaluate the participant for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

The ECG measurement may be performed by an MN professional.

8.2.4 Clinical Safety Laboratory Tests

See Appendix 6 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (see Section 1.3) for the timing and frequency. Clinical laboratory tests conducted by a central laboratory must be conducted in accordance with the laboratory manual.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event CRF (see Appendix 2).

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 12 months of the final dose of study treatment should be repeated until the values return to normal or baseline or are considered to be stable and no longer considered clinically significant by the investigator or Medical Monitor.

If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the Sponsor notified.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., serious adverse event or adverse event or dose modification), the results must be recorded on the eCRF.

Sample collection may be performed by an MN professional.

Samples collected for safety laboratory tests will be destroyed no later than the time of completion of the final Clinical Study Report.

8.2.5 Pregnancy Testing

The schedule for pregnancy testing for enrolled female participants of child-bearing potential is outlined in Section 1.3 and will be conducted as outlined in Appendix 6.

8.3 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

The definitions of adverse event and serious adverse event can be found in Appendix 2.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or serious adverse event and remain responsible for following up adverse events that are serious, are considered related to the study treatment or study procedures, or caused the participant to discontinue the study treatment/study (see Section 7).

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

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 (see Appendix 2). All other medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the General Medical History and Baseline Conditions eCRF, not the Adverse Event eCRF.

All adverse events will be reported from the start of treatment until 12 months after the final dose of obinutuzumab and until 6 weeks after the final dose of MMF at the timepoints specified in the Schedule of Activities (see Section 1.3).

All serious adverse events will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 2. The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek adverse event or serious adverse event information after conclusion of study participation. However, if the investigator learns of any serious adverse event, including a death, at any time after a participant has been discharged from the study, and he or she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 2.

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about adverse event occurrences.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each participant at subsequent visits or contacts.
All adverse events will be followed until the event has resolved to baseline grade or better, or the event is assessed as stable by the investigator, or the participant is lost to follow-up (as defined in Section 7.3), or the participant withdraws consent. Further information on follow-up procedures is provided in Appendix 2.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification (i.e., within 24 hours of awareness) by the investigator to the Sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/Ethics Committees (ECs), and investigators.

For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

To determine reporting requirements for serious 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 Investigator's Brochure
MMF	Cellcept® 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.

An investigator who receives an investigator safety report describing a serious adverse event or other specific safety information (e.g., summary or listing of serious adverse events) from the Sponsor will review and then file it along with the Investigator's Brochure/European Union Summary of Product Characteristics and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5 Pregnancy

Female participants 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 and for 6 weeks after the final dose of MMF.

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if a female partner becomes pregnant during the study or within 90 days after the final dose of MMF.

If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Appendix 4. 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.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

8.3.6 Cardiovascular and Death Events

Information on reporting deaths is provided in Appendix 2.

8.3.7 Anticipated Events Not Qualifying for Expedited Reporting

Events not qualifying for expedited reporting will not be defined for this study.

8.3.8 Adverse Events of Special Interest

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 the investigator becomes aware of the event; see Appendix A2–5 for reporting instructions). Adverse events of special interest *(AESI)* 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 Appendix A2–7.7)
- Suspected transmission of an infectious agent by a study treatment, 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 participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

In addition to the above study level AESIs, AESIs for Obinutuzumab include the following:

- *IRRs; Systemic IRRs only (local IRRs are not considered AESI).*
- Grade ≥3 (severe, life-threatening, or fatal) infections
- Any hepatitis B reactivation
- Progressive multifocal leukoencephalopathy
- Study drug–related neutropenia
- Study drug–related thrombocytopenia
- Gastrointestinal perforations
- Worsening of preexisting cardiac conditions

Descriptions of risks and management of the above-listed adverse events are provided in Appendix 3.

8.3.9 Medical Monitors and Emergency Medical Contacts

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

8.4 PHARMACOKINETICS

Blood samples of approximately 2 mL will be collected for measurement of serum concentrations of obinutuzumab as specified in the Schedule of Activities (see Section 1.3).

Samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the Sponsor. The timing of sampling may be altered during the course of the study on the basis of newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the pharmacokinetics of obinutuzumab. Samples collected for analyses of obinutuzumab serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained. At visits during which blood samples for the determination of serum obinutuzumab will be taken, one sample of sufficient volume can be used.

PK samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed to allow for assay development and validation (if needed).

8.5 PHARMACODYNAMICS

PD analyses may be conducted. See Section 8.7 for information on pharmacodynamic biomarkers.

8.6 GENETICS

Genetic biomarker assessments will not be performed in this study.

8.7 BIOMARKER ASSESSMENTS

The following biomarker samples will be collected, as applicable, from participants at all sites:

- Whole blood samples for the determination of peripheral B cell and B cell subsets (e.g., memory B cells) for the characterization of obinutuzumab-induced pharmacodynamic changes

[redacted]

8.9 HEALTH ECONOMICS AND MEDICAL RESOURCE UTILIZATION

Health economics and medical resource utilization assessments will not be performed in this study.

8.10 ADDITIONAL ASSESSMENTS AND PROCEDURES REQUIRING SEPARATE CONSENT OR PERFORMED ONLY AT PARTICIPATING SITES

There are no additional assessments and procedures requiring separate consent or performed only at participating sites.

9. STATISTICAL CONSIDERATIONS

Formal statistical hypotheses will be tested for this study. Results on endpoints will be summarized.

9.1 STATISTICAL HYPOTHESES

The primary efficacy analysis for this study will compare obinutuzumab with MMF based on the proportion of patients who remain in sustained complete remission (first morning void UPCR ≤0.2 g/g) at Week 52 without occurrence of a relapse or any of the intercurrent events listed in Section 9.5.2.1

The following null and alternative hypothesis will be tested at a two-sided 0.05 significance level, which is equal to a 0.025 one-sided test for superiority:

$$H_0: P_{Obinutuzumab} = P_{MMF} \text{ versus } H_a: P_{Obinutuzumab} \neq P_{MMF}$$

For which $P_{Obinutuzumab}$ and P_{MMF} refer to the proportion of participants who achieve sustained CR at Week 52, without intercurrent events *(except for treatment discontinuation due to AE or any reason other than lack of efficacy)* after the initial prednisone taper, for obinutuzumab and MMF respectively. The definition of intercurrent events can be found in Table 5.

Primary and secondary endpoints will be tested to compare the obinutuzumab arm with the MMF arm for the superiority of obinutuzumab over MMF. To control *for* multiplicity for the overall type I error *rate*, a fixed sequence testing procedure will be used (Westfall and Krishen 2001). The primary and key secondary endpoints will be tested in *a fixed* order at a two-sided 5% significance level, proceeding sequentially starting from the primary endpoint and testing each *key-secondary endpoint in order,* after achieving statistical significance on the previous endpoint. *The exact sequence order for endpoint testing will be specified in the SAP.*

9.2 SAMPLE SIZE DETERMINATION

Approximately 80 participants aged ≥2–25 years old will be enrolled into the study and randomized in a 1:1 ratio to one of the two open-label treatment groups:

- Obinutuzumab (Group A) or
- MMF (Group B)

Randomization will be stratified by the participant's disease type (FRNS vs. SDNS) and the use of immunosuppressive treatment, other than corticosteroids for INS prior to study entry (MMF/other immunosuppressive agent vs. no use of MMF/other immunosuppressive agent). Randomized participants will receive either an infusion of obinutuzumab 1000 mg IV on Days 1, 15, 168 (Week 24), and Day 182 (Week 26), during the initial 52-week treatment period[2] or commence or continue daily oral MMF (either tablet, capsule, or liquid formulation) on Day 1.

[2] Participants with a body weight of 45 kg or more will receive the 1000 mg obinutuzumab dose. Participants with a body weight below 45 kg will receive a weight adjusted dose of 20 mg/kg for obinutuzumab infusions.

Participants in both treatment groups may receive a tapering course of oral corticosteroids in addition to their randomized treatment (see Section 6.1.3).
The primary endpoint of this study is the Proportion of Participants with Sustained Complete Remission at 1 year, defined as first morning void UPCR ≤0.2 g/g at Week 52 without occurrence of a relapse or *other* intercurrent event *as listed in Section 9.5.2.1.*
Assuming 72.5% of participants in the obinutuzumab group and 40% participants in the MMF group remain in complete remission and free from relapsing and intercurrent events at 1 year, a total of approximately 80 participants (40 in each group) under 1:1 randomization with two stratification factors will provide about 85% power using Cochran-Mantel-Haenszel (CMH) test assuming equal strata size at the two-sided 5% significance level.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

9.3 ANALYSIS SETS

The following analysis sets are defined:

Table 8 Analysis Population Definition

Analysis Set	Definition
Efficacy-Evaluable	All randomized patients, whether or not the patient received the assigned treatment. Patients will be grouped and analyzed according to the treatment assignment at the time of randomization rather than the treatment received.
Safety-Evaluable	All participants who received any amount of study drug. Participants will be grouped and analyzed according to the treatment they actually received.
PK-evaluable	The PK-evaluable set will include all participants in the Efficacy-Evaluable set who have received any dose of obinutuzumab given as study drug, have at least one post-dose PK sample that is evaluable, and have no major protocol deviations that would impact the PK results. All PK analyses will be performed using the PK evaluable set.

PK=pharmacokinetic.

9.4 STATISTICAL ANALYSES

The Statistical Analysis Plan (SAP) will be finalized prior to the primary efficacy analysis and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses for primary and key secondary endpoints.

9.5 PRIMARY ENDPOINT

9.5.1 General Considerations

Statistical hypothesis testing will be conducted on the primary endpoint and secondary endpoints at the two-sided 5% significance level. All endpoints will be summarized descriptively. For binary endpoints, difference in proportions will be estimated, along with its 95% CI. *Nominal p-values will be presented using 2-sided tests at a 5% significance level.* Summary statistics, including mean, median, standard deviation, and range, will be reported for continuous endpoints.

Baseline is defined as the last non-missing value prior to the receipt of any dose of study treatment. Baseline will be the pre-dose Day 1 assessment. If it is missing or not available, screening results will be used as baseline values.

In general, the following events (not limited) are considered intercurrent events: relapse, any systemic corticosteroids usage (for > 14 days in a 30 day period), initiation of any rescue therapy for INS, as determined by the Investigator's best medical judgment, other than systemic corticosteroids, treatment discontinuation due to lack of efficacy, *treatment discontinuation due to adverse event or any reason (other than lack of efficacy),* and death. The definition of intercurrent events can be found in Table 5. The methods to handle the intercurrent events are provided with the description of the estimands for the primary and key secondary endpoints, respectively.

9.5.2 Primary Endpoint(s)

9.5.2.1 Definition of Primary Endpoint(s)

The primary objective for this study is to evaluate the efficacy of obinutuzumab compared with MMF.

The estimand attributes of the primary endpoint for efficacy analysis are as follows:

Population: All patients with FRNS or SDNS.

Treatments: Obinutuzumab arm or MMF arm

- Obinutuzumab arm (Group A): Obinutuzumab 1000 mg IV on Days 1, 15, 168 (Weeks 24), and Day 182 (Week 26)
- MMF arm (Group B): 600 mg/m^2 BID (target 1200 mg/m^2/day in divided doses, maximum 2 g/day) to Week 52

Variable: Proportion of Participants with Sustained Complete Remission at 1 year, defined as first morning void UPCR ≤0.2 g/g at Week 52 without occurrence of relapse or any *other* intercurrent event .

Intercurrent Events:

Intercurrent events occurring after Week 8:

- Relapse as defined by any of the following events:
  - First-morning void UPCR ≥2 g/g **or**

- Dipstick UA ≥3+ for 3 consecutive days (home-monitoring) and the most recent urine sample determined to have UPCR >0.2 g/g as measured by the central laboratory **or**
- Dipstick UA protein ≥3+ on any single day with edema and urine sample determined to have UPCR >0.2 g/g as measured by the central laboratory

- Any systemic corticosteroids usage for >14 days in a 30 day period [3]

Intercurrent events occurring after randomization:

- Initiation of any rescue therapy for INS, as determined by the investigator's best medical judgement, other than systemic corticosteroids
- Treatment discontinuation due to lack of efficacy
- Death

Strategy for Intercurrent Events: [redacted]

Population-level summary measure: Difference in the proportion of sustained CR at Week 52 will be used to summarize the treatment effect between obinutuzumab and MMF arms at the time of the primary analysis, which occurs after all participants have either completed the Week 52 study visit assessments or have discontinued from the study prior to Week 52 assessment.

Main Analytical Approach: The proportion of sustained CR at 1 year (Week 52) between obinutuzumab and MMF arms will be reported as the difference with 95% CI calculated based on the normal approximation of the binary distribution. The statistical test for significance will be performed using the CMH test *at 5% level of significance (two-sided), with disease type and use of immunosuppressive treatment prior to study entry (other than corticosteroids for INS) as stratification factors.*

Missing *Data:* [redacted]

[3] *Participants who do not complete the protocol-defined steroid taper (i.e., still receiving systemic corticosteroid after Week 8 for more than 14 days in a 30-day period) will be treated as non-responders for binary outcomes and events for overall RFS.*

Details of the statistical methodologies for analysis, including the specification of multiple imputation and sensitivity analysis for assessing the robustness of the results, will be specified in the SAP.

9.5.3 *Key/Confirmatory* Secondary Endpoints

Estimand attributes and analytical approaches are outlined below. Details of the analysis will be fully specified in the SAP.

9.5.3.1 *Time-to-Event Key Secondary Endpoints*

The estimand attributes for time-to-event key secondary endpoints are defined as follows:

Population: *See Section 9.5.2.1.*

Treatments: *See Section 9.5.2.1.*

Variable:

- Overall RFS (including all available data at the clinical cut-off date) defined as the time from randomization to first relapse or any of the following intercurrent events including death, treatment discontinuation due to lack of efficacy, initiation of any rescue therapy for INS, as determined by the investigator's best medical judgement, other than systemic corticosteroids, failing to complete the protocol-defined steroid taper, *and any systemic corticosteroid usage for >14 days in a 30-day period outside of the protocol defined steroid taper, whichever occurs first, and excluding treatment discontinuation due to adverse event or any reason (other than lack of efficacy).*
- *Probability of RFS at Week 52 is defined as the proportion of participants remaining free of relapse or any other intercurrent events (except for treatment discontinuation due to AE or any reason other than lack of efficacy) at Week 52. Intercurrent events and handling are defined the same as RFS.*

Intercurrent events:

The following intercurrent events are treated as the part of the definition of this time-to-event endpoint described above:

- Death
- Treatment discontinuation due to lack of efficacy
- Initiation of any rescue therapy for INS, as determined by the investigator's best medical judgement, other than systemic corticosteroids
- Failing to complete the protocol-defined steroid taper
- *Any* systemic corticosteroid usage for >14 days in a 30-day period, *outside* of the *protocol defined* steroid taper

[redacted]

- [redacted]
- [redacted]

[redacted]

- [redacted]

Population-level summary measure:

- *Overall RFS: hazard Ratio (HR) and log-rank test*
- *Probability of RFS at Week 52: difference in probability of RFS at Week 52*

Main Analytical Approach: Details of the analysis will be specified in the SAP.

Missing Data: Details of the missing data handling will be specified in the SAP.

9.5.3.2 *Binary Key Secondary Endpoints*

The estimand attributes for binary *key* secondary endpoints are defined as follows:

Population: *See Section 9.5.2.1.*

Treatments: *See Section 9.5.2.1.*

Variable:

- *Proportion of participants experiencing edema-associated relapse during the 52-week treatment period defined as the proportion of participants who have experienced an edema-associated relapse[4] without occurrence of an intercurrent event as defined by the primary endpoint (see Section 9.5.2.1), prior to Week 52.*
- *Proportion of participants in sustained complete remission at Week 76, defined as first morning void UPCR ≤0.2 g/g at Week 76 without occurrence of an intercurrent event as defined by the primary endpoint (see Section 9.5.2.1).*

Intercurrent Events: *See Section 9.5.2.1.*

[4] *Edema-associated relapse definition is the same as the definition of relapse for the primary endpoint except that the edema-associated relapse definition additionally requires that patient edema is present and documented in the eCRF at the time of the relapse event.*

Population-level summary measure:

- *Proportion of participants experiencing edema-associated relapse during the 52-week treatment period: difference in proportion between the obinutuzumab and MMF treatment arms*
- *Proportion of participants in sustained complete remission at Week 76: difference in proportion between the obinutuzumab and MMF treatment arms among Week-76 evaluable participants.*

Main Analytical Approach: Details of the analysis will be specified in the SAP.

Missing Data: Details of the missing data handling will be specified in the SAP.

9.5.3.3 *Continuous/Count Key Secondary Endpoints*

The estimand attributes for continuous/*count key* secondary endpoints are defined as follows:

Population: *See Section 9.5.2.1.*

Treatments: *See Section 9.5.2.1.*

Variable:

- *Clinical outcome assessment (edema severity/general fatigue/physical functioning) from baseline to Week 52 defined as the mean change from baseline to Week 52, regardless of relapse, systemic corticosteroids usage for > 14 days in a 30 day period, and treatment discontinuation due to any reason, in patients prior to receiving rescue therapy and assuming death has not occurred. See Section 8.1.2 for derivation of these scales.*
- *Cumulative corticosteroid dose defined as the total dose received (mg) of prednisone or equivalent adjusted for time on study from baseline to Week 52, regardless of intercurrent events (relapse, rescue therapy, treatment discontinuation for any reason, and systemic corticosteroid usage for > 14 days) in patients prior to experiencing death.*
- *Number of relapses defined as an adjusted rate ratio from baseline to Week 52, regardless of intercurrent events (relapse, treatment discontinuation for any reason, and systemic corticosteroid usage for > 14 days) in patients prior to receiving rescue therapy or experiencing death.*

Intercurrent events:

- Relapse
- Any systemic corticosteroids usage for > 14 days in a 30 day period
- Initiation of any rescue therapy for INS, as determined by the investigator's best medical judgement, other than systemic corticosteroids

- Treatment discontinuation due to lack of efficacy
- *Treatment discontinuation due to adverse event or any reason (other than lack of efficacy)*
- Death

Strategy for Intercurrent Events for Continuous Endpoints (except for the endpoint of cumulative corticosteroid dose *and number of relapses, which are specified separately below):*

- *Treatment Policy Strategy will be used to deal with relapse, systemic corticosteroids usage for > 14 days in a 30 day period, and treatment discontinuation for any reason.* While-on-Treatment Strategy will be used to deal with *the initiation of any rescue therapy for INS, as determined by the investigator's best medical judgement, other than systemic corticosteroids.*
- Hypothetical Strategy will be used to deal with death.

Strategy for Intercurrent Events for Cumulative Corticosteroid Dose:

- *All intercurrent events, except death, will be dealt with using the treatment policy strategy. A while-on-treatment strategy will be used for death.*

Strategy for Intercurrent Events for Number of Relapses:

- *All intercurrent events, except death and rescue therapy, will be dealt with using the treatment policy strategy. A while-on-treatment strategy will be used for rescue therapy and death.*

Population-level summary measure:

- *Cumulative corticosteroid dose: difference in medians between obinutuzumab and MMF treatment arms.*
- *Number of relapses: adjusted rate ratio between obinutuzumab and MMF arms.*
- *Mean change in (CureGN Edema/General Fatigue/Physical Functioning) Scale from baseline to Week 52: difference in adjusted means between obinutuzumab and MMF arms*

Main Analytical Approach: Details of the analysis will be specified in the SAP.

Missing Data: Details of the missing data handling will be specified in the SAP.

Details of the statistical methodologies for analyzing key secondary endpoints, including the specification of multiple imputation, will be provided in SAP.

Safety analyses will be performed on the safety-evaluable population as defined in Section 9.3.

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs.

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

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0 or most current CTCAE version available. The eCRF will also capture categorization of adverse events as mild, moderate, severe or life-threatening, based on the investigator's clinical judgment. 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, and temperature), and ECG data 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 post-baseline severity grade. Changes in vital signs and ECGs will be summarized.

9.5.4 Exploratory Endpoints

[redacted]

9.5.4.1 Summaries of Conduct of Study

The number of participants who enroll, discontinue, and complete the study will be summarized by treatment arm and study period. The reasons for study treatment discontinuation will also be tabulated. Major protocol deviations, including major deviations with regards to the inclusion and exclusion criteria, will be summarized by treatment arm.

9.5.4.2 Summaries of Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment arm. Baseline data are the last data obtained prior to initiation of study treatment. Descriptive statistics (mean, standard deviation, median, and range) will be presented for continuous variables and counts and *proportions* will be presented for categorical variables. *The full list of variables are detailed in the SAP.*

9.5.4.3 Pharmacokinetic Analyses

Serum concentrations of obinutuzumab 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. Pharmacokinetic profile data will be used to further develop a population PK model describing obinutuzumab PK following IV administration to participants with FRNS or SDNS, including the effect of major covariates on the main parameters (e.g., clearance).

Derivation of individual measures of exposure such as area under the serum concentration time curve (AUC) and maximum serum concentration (C_{max}) will depend on the final model used for the analysis. Exploratory graphical analyses will be performed to assess the relationships between obinutuzumab exposure and efficacy and 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 logistical regression analyses and indirect response modeling. Additional PK and PD analyses may be conducted as appropriate. Results of the population PK and exploratory exposure-response and PD analyses may be reported separately.

Additional PK and PD analyses may be conducted as appropriate.

The following biomarker samples will be collected, as applicable, from participants at all sites:

- Whole blood samples for the determination of peripheral B cell and B cell subsets (e.g., memory B cells) for the characterization of Obinutuzumab-induced pharmacodynamics

[redacted]

[redacted]

[redacted]

9.6 INTERIM ANALYSIS/ANALYSES

There is no interim analysis planned for this study.

9.7 CHINA SUBPOPULATION ANALYSES

The China subpopulation will include all patients enrolled at China's sites. Results from these analyses will be summarized in an addendum to the Clinical Study Report.

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Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

Table of Contents

A1–1 Regulatory and Ethical Considerations 104
A1–2 Financial Disclosure 104
A1–3 Informed Consent Process 105
A1–4 Data Protection 105
A1–5 Administrative Structure 106
A1–6 Dissemination of Clinical Study Data 106
A1–7 Data Quality Assurance 107
A1–8 Source Documents 108
A1–9 Study and Site Closure 108
A1–10 Publication Policy 109
A1–11 Protocol Deviations 109

A1–1 REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable International Council for Harmonisation (ICH) Guideline for Good Clinical Practice
- Applicable laws and regulations

The protocol, Informed Consent Form, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board or Ethics Committee (IRB/EC) by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study participants. The investigator will be responsible for the following:

- 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
- Notifying the IRB/EC of serious adverse events or other significant safety findings, as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and ensuring adherence to requirements of 21 CFR (U.S. sites only), the ICH Guideline for Good Clinical Practice, the IRB/EC, *Clinical Trials Directive (2001/20/EC) or Clinical Trials* Regulation 536/2014 (*EEA* sites only), and all other applicable local regulations

A1–2 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 study and for 1 year after completion of the study (see definition of end of study in Section 4.4).

A1–3 INFORMED CONSENT PROCESS

The investigator or authorized designee will explain the nature of the study, including the risks and benefits, to the participant or his or her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (U.S. sites only), the ICH Guideline for Good Clinical Practice, and the IRB/EC.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. Informed consent must be documented before any study-specific screening procedure are performed. The authorized person obtaining the informed consent must also sign the Informed Consent Form.

If the Informed Consent Form is revised (through an amendment or an addendum) to communicate information that might affect a participant's willingness to continue in the study, the participant or the participant's legally authorized representative must re-consent by signing the most current version of the Informed Consent Form or the addendum, in accordance with applicable laws and IRB/EC policy.

A copy of each Informed Consent Form must be provided to the participant or the participant's legally authorized representative.

A1–4 DATA PROTECTION

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.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; the participant's name or any information that would make the participant identifiable will not be transferred.

Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to participants, who will be required to give consent for their data to be used as described in the Informed Consent Form.

Participants must be informed that their medical records may be examined by auditors or other authorized individuals representing the Sponsor or Sponsor collaborators and licensees, by appropriate IRB/EC members, and by inspectors from health authorities.

A1–5 ADMINISTRATIVE STRUCTURE

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

Approximately 60 sites globally will participate to enroll approximately 80 participants. Enrollment will occur through an interactive voice or web-based response system.

Central facilities will be used for certain assessments throughout the study (e.g., specified laboratory tests, biomarker and pharmacokinetic analyses), as specified in Section 8 and Appendix 6 . Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An Independent Data Monitoring Committee (iDMC) will be formed to monitor and evaluate participant safety throughout the study. The committee will attend regular safety review meetings and provide input and advice on appropriate monitoring of safety throughout the study.

A1–6 DISSEMINATION OF CLINICAL STUDY DATA

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/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 provided 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/

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

A1–7 DATA QUALITY ASSURANCE

The Sponsor 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.

All participant data relating to the study will be recorded on printed or electronic Case Report Forms (CRFs) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided prior to study initiation, in the various functional monitoring plans (including, but not limited to, Quality Tolerance Limit Management Plan and Trial Monitoring Plan).

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Study monitors will perform ongoing monitoring activities as specified in the Trial Monitoring Plan to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH Guideline for Good Clinical Practice, and all applicable regulatory requirements.

Records and documents pertaining to the conduct of this study, including signed Informed Consent Forms, must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written

approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A1–8 SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the electronic Case Report Form (eCRF) that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in the Trial Monitoring Plan.

A1–9 STUDY AND SITE CLOSURE

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to, the following:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or the ICH Guideline for Good Clinical Practice
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

A1–10 PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of results of multicenter studies only in their entirety and not as individual site 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.

A1–11 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any *major* deviations that might have an impact on participant 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 *major* 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.

Appendix 2
Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

Table of Contents

A2–1 Definition of Adverse Event 111
A2–2 Definition of Serious Adverse Event 112
A2–3 Recording and Follow-Up of Adverse Events AND Serious Adverse Events 113
A2–3.1 Adverse Event and Serious Adverse Event Recording 113
A2–3.2 Assessment of Severity 114
A2–3.3 Assessment of Causality 115
A2–3.4 Follow-up of Adverse Events and Serious Adverse Events 116
A2–3.4.1 Investigator Follow-Up 116
A2–3.4.2 Sponsor Follow-Up 117
A2–4 Reporting of Serious Adverse Events 117
A2–4.1 Serious Adverse Event Reporting to the Sponsor via an Electronic Collection Tool 117
A2–4.2 Serious Adverse Event Reporting to the Sponsor via Paper CRF 117
A2–5 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest 118
A2–5.1 Events That Occur Prior to Study Treatment Initiation 118
A2–5.2 Events That Occur After Study Treatment Initiation 118
A2–6 Reporting Adverse Events That Occur after the Adverse Event Reporting Period 118
A2–7 Procedures for Recording Adverse Events 119
A2–7.1 Infusion-Related Reactions 119
A2–7.2 Diagnosis Versus Signs And Symptoms 119
A2–7.3 Adverse Events that are Secondary to Other Events 120
A2–7.4 Persistent or Recurrent Adverse Events 120
A2–7.5 Abnormal Laboratory Values 121
A2–7.6 Abnormal Vital Sign Values 121
A2–7.7 Abnormal Liver Function Tests 122
A2–7.8 Deaths 122
A2–7.9 Preexisting Medical Conditions 123
A2–7.10 Lack of Efficacy or Worsening of Idiopathic Nephrotic Syndrome 123
A2–7.11 Hospitalization or Prolonged Hospitalization 124
A2–7.12 Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse 124

A2–1 DEFINITION OF ADVERSE EVENT

Adverse Event Definition

An adverse event is any untoward medical occurrence in a patient or clinical study participant temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the Adverse Event Definition

The following events meet the definition of adverse event:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study treatment administration, even though it may have been present before the start of the study
- Signs, symptoms, or clinical sequelae of a suspected drug–drug interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study treatment or a concomitant medication
  - Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal or self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments.

Events NOT Meeting the Definition of Adverse Event

The following events do not meet the definition of adverse event:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition

- Medical or surgical procedure (e.g., endoscopy, appendectomy)
  - The condition that leads to the procedure is the adverse event.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of a preexisting disease or condition present or detected at the start of the study that do not worsen

A2–2 DEFINITION OF SERIOUS ADVERSE EVENT

If an event is not an adverse event per the definition in A2–1, it cannot be a serious adverse event even if serious conditions are met (e.g., hospitalization for signs or symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
  - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
  - In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious.
  - Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event.
- Results in persistent disability or incapacity
  - The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect
- Other situations:
  - Medical or scientific judgment should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE]; see Section A2–3.2); 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 electronic Case Report Form (eCRF).

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event) (see Section A2–5 for reporting instructions).

A2–3 RECORDING AND FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A2–3.1 ADVERSE EVENT AND SERIOUS ADVERSE EVENT RECORDING

When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant adverse event or serious adverse event information on the electronic Caser Report Form (eCRF).

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs or symptoms) will be documented as the adverse event or serious adverse event.

A2–3.2 ASSESSMENT OF SEVERITY

The investigator will assess the clinical significance and intensity of each adverse event reported during the study according to a four point scale (mild, moderate, severe, life-threatening) (see Table A2-1 for intensity definitions) and this will be recorded in the adverse event eCRF. In addition, NCI-CTC AE Grade will be recorded, if applicable, through use of the NCI CTCAE (v 5.0) grading scale. The investigator will use the definitions and grading scale in Table A2-1 for assessing the severity of adverse events that are not specifically listed in the NCI CTCAE.

The eCRF will capture categorization of adverse events based on the investigator's clinical judgment of severity beyond the NCI CTCAE grading per Table A2-1.

Table A2-1 Adverse Event Severity Grading Scale

Intensity	Grading	Definitions
Mild	1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated.
Moderate	2	Minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living.
Severe	3	Medically significant [a], but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living. [b]
Life-threatening	4	Life-threatening consequences or urgent intervention indicated. [c]

Note: Based on the most recent version of NCI CTCAE (v 5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section A2–5 for reporting instructions), per the definition of serious adverse event in Section A2–2.

[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 participants who are not bedridden.

[c] Grade 4 events must be reported as serious adverse events (see Section A2–5 for reporting instructions), per the definition of serious adverse event in Section A2–2.

A2–3.3 ASSESSMENT OF CAUSALITY

The investigator is obligated to assess the relationship between study treatment and each occurrence of each adverse event or serious adverse event.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.

The investigator will also consult the Investigator's Brochure and/or prescribing information (for marketed products) in his or her assessment.

For each adverse event or serious adverse event, the investigator **must** document in the medical notes that he or she has reviewed the adverse event or serious adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred, and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data to the Sponsor.

The investigator may change his or her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

A2–3.4 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A2–3.4.1 Investigator Follow-Up

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor with a copy of any post-mortem findings, including histopathology.

New or updated information should be recorded on the originally completed Adverse Event eCRF. 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 the investigator becomes 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 even

During the adverse event reporting period (defined in Section 8.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification.

A2–3.4.2 Sponsor Follow-Up

For serious adverse events and adverse events of special interest, 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.

A2–4 REPORTING OF SERIOUS ADVERSE EVENTS

A2–4.1 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA AN ELECTRONIC COLLECTION TOOL

The primary mechanism for reporting a serious adverse event to the Sponsor will be the electronic data collection tool, as described in Section A2–5.

If the electronic system is unavailable, the site will use the paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A2–5, to report the event within 24 hours.

The site will enter the serious adverse event data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

If a site receives a report of a new serious adverse event from a study participant or receives updated data on a previously reported serious adverse event after the electronic data collection tool has been taken off line, the site can report this information on a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A2–5.

A2–4.2 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA PAPER CRF

Under certain circumstances, serious adverse events may be reported to the Sponsor through use of a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A2–5.

A2–5 REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS OF SPECIAL INTEREST

A2–5.1 EVENTS THAT OCCUR PRIOR TO STUDY TREATMENT INITIATION

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., biopsy, discontinuation of medications) 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 the investigator becomes aware of the event), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators.

A2–5.2 EVENTS THAT OCCUR AFTER STUDY TREATMENT INITIATION

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 12 months after the final dose of obinutuzumab, until 6 weeks after the final dose of MMF, or longer for participants who require a greater duration of follow-up after the final dose of study treatment. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after the investigator becomes aware 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 the investigator becomes aware 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 more than 12 months after the final dose of obinutuzumab and 6 weeks after the final dose of MMF are provided in Section A2–6.

A2–6 REPORTING 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 (defined as 12 months after the final dose of obinutuzumab; 6 weeks after the final dose of MMF; or

longer for participants who require a greater duration of follow-up after the final dose of study treatment), if the event is believed to be related to prior exposure to study 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.

A2–7 PROCEDURES FOR RECORDING ADVERSE EVENTS

When an adverse event occurs, it is the responsibility of the investigator to review all documentation related to the event (e.g., hospital progress notes, laboratory reports, and diagnostics reports). The investigator will then record all relevant adverse event information on the Adverse Event eCRF. It is not acceptable for the investigator to send photocopies of the participant's medical records to the Medical Monitor in lieu of completion of the eCRF. Investigators should use correct medical terminology and 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 of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

A2–7.1 INFUSION-RELATED REACTIONS

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

A2–7.2 DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

For adverse events other than infusion-related reactions (see Section A2–7.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs

and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

A2–7.3 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.

A2–7.4 PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between participant 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 the investigator becomes aware that the event became serious; see Section A2–5 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 participant evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

A2–7.5 ABNORMAL LABORATORY VALUES

Not every abnormal laboratory value qualifies as an adverse event. A laboratory value abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected.
A laboratory value abnormality that is not associated with the underlying disease 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., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × upper limit of normal (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 A2–7.4 for details on recording persistent adverse events).

A2–7.6 ABNORMAL VITAL SIGN VALUES

Not every abnormal vital sign value qualifies as an adverse event. A vital sign abnormality that is associated with the underlying disease should not be reported as an

adverse event unless judged by the investigator to be more severe than expected. A vital sign abnormality that is not associated with the underlying disease 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., dose 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 (e.g., 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 A2–7.4 for details on recording persistent adverse events).

A2–7.7 ABNORMAL LIVER FUNCTION TESTS

The finding of an elevated ALT or AST (>3× ULN) in combination with either an elevated total bilirubin (>2× 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× ULN in combination with total bilirubin >2× ULN
- Treatment-emergent ALT or AST >3× 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 A2–7.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either as a serious adverse event or an adverse event of special interest (see Section A2–5).

A2–7.8 DEATHS

All deaths that occur during the protocol-specified adverse event reporting period (see Section 8.3.1), regardless of relationship to study treatment, must be recorded on

the Adverse Event eCRF and immediately reported to the Sponsor (see Section A2–5). This includes death attributed to progression of idiopathic nephrotic syndrome.

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 idiopathic nephrotic syndrome, "idiopathic nephrotic syndrome progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section A2–6.

A2–7.9 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").

A2–7.10 LACK OF EFFICACY OR WORSENING OF IDIOPATHIC NEPHROTIC SYNDROME

Deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature (i.e., deterioration beyond the expected pattern of progression of the underlying disease) should be recorded as an adverse event. When recording an unanticipated worsening of idiopathic nephrotic syndrome on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of idiopathic nephrotic syndrome"). Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected

pattern of progression will be based on frequent relapse. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

A2–7.11 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 A2–2), except as outlined below.

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The participant was hospitalized for an elective procedure that was planned prior to the study, was scheduled during the study despite the fact that the condition had not worsened, or was scheduled during the study when treatment became necessary because of the expected normal progression of the condition
  - The participant has not experienced an adverse event
- Hospitalization due solely to progression of idiopathic nephrotic syndrome

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 participant requirement for outpatient care outside of normal outpatient clinic operating hours

A2–7.12 CASES OF OVERDOSE, MEDICATION ERROR, DRUG ABUSE, OR DRUG MISUSE

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 the investigator becomes aware of the event; see Section A2–5). For obinutuzumab 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, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter obinutuzumab 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 obinutuzumab 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 obinutuzumab 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.

REFERENCES

NCI CTCAE v5.0. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed on 1 Aug 2022.

Appendix 3
Safety Plan: Management of Identified and Potential Risks

Table of Contents

A3–1 Risks Associated with Obinutuzumab 128
A3–1.1 Infusion-Related Reactions 128
A3–1.2 Infections 129
A3–1.3 Hepatitis B Reactivation 130
A3–1.4 Progressive Multifocal Leukoencephalopathy 130
A3–1.5 Immunizations 130
A3–1.6 Drug-Related Neutropenia 130
A3–1.7 Drug-Related Thrombocytopenia 131
A3–1.8 Coagulation abnormalities including disseminated intravascular coagulation (DIC) 131
A3–1.9 B-Cell Depletion and Recovery 131
A3–1.10 Immunoglobulin Depletion and Recovery 132
A3–1.11 Gastrointestinal Perforation 134
A3–1.12 Worsening of Preexisting Cardiac Conditions 134
A3–2 Risks Associated with MMF 134
A3–3 Management of Participants Who Experience Adverse Events 134
A3–3.1 Dose Modifications 134
A3–3.2 Treatment Interruption 135
A3–3.3 Management Guidelines 135

A3–1 RISKS ASSOCIATED WITH OBINUTUZUMAB

Obinutuzumab is currently approved for the treatment of chronic lymphocytic leukemia (CLL) and follicular lymphoma (FL) and clinical development is ongoing in other malignancies such as non-Hodgkin lymphoma (NHL) as well as autoimmune diseases. The safety plan for participants 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. 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 study participants. Eligibility criteria have been designed to exclude individuals at higher risk for toxicities. Participants 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.

A3–1.1 INFUSION-RELATED REACTIONS

The most frequently observed adverse drug reactions in participants who received obinutuzumab during clinical studies in CLL and NHL were infusion-related reactions (IRRs), which occurred predominantly during infusion of the first 1000 mg.
In participants who received the combined measures for prevention of IRRs at first infusion (glucocorticoid, oral analgesic/antihistamine premedication, omission of antihypertensive medication in the morning of the first infusion, and, for CLL participants only, the Day 1, Cycle 1 dose administered over 2 days), a decreased incidence of all grade IRRs was observed. The rates of Grades 3 and 4 IRRs (which were based on a relatively small number of participants) 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 participants having no infusion-related reactions (IRRs) during subsequent administrations of obinutuzumab.

In the majority of participants, 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 participants received either obinutuzumab or rituximab (another anti-CD20 monoclonal antibody), obinutuzumab-treated participants appeared to have more IRRs compared with participants receiving rituximab in participants being treated for hematologic malignancies.

In the NOBILITY study in participants with lupus nephritis (LN), 10 participants (15.6%) in the obinutuzumab plus mycophenolate mofetil (MMF) arm experienced IRRs (vs. 6 participants [9.8%] in the placebo plus MMF arm) during the 52-week treatment period. All IRRs in the obinutuzumab arm were non-serious and except for one Grade 3 IRR were all of Grade 1 or 2. Of the 10 participants, the IRRs occurred at the first infusion in 8 participants; all IRRs resolved and none led to obinutuzumab discontinuation.

Guidelines for management of participants who develop IRRs are provided in Section A3–3.3.

A3–1.2 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 vs. chlorambucil alone) and Stage 2 (obinutuzumab + chlorambucil vs. rituximab + chlorambucil) of Study BO21004 in participants with CLL, the incidence of infections was similar between the treatment arms. However, compared with the obinutuzumab + chlorambucil arm, participants in the 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 in participants with LN, at the Week 104 data cutoff, a higher incidence of all infections (serious and non-serious) was observed with obinutuzumab compared with placebo (75% vs. 62.3%). However, the placebo arm showed higher incidences of Grade ≥ 3 infection (21.3% vs. 6.3%) and serious infections (18% vs. 7.8%) compared to the obinutuzumab arm. Through Week 104, the incidence of infections (serious and non-serious) was 75% versus 62% with obinutuzumab and placebo, respectively.

Guidelines for management of participants who develop infections are provided in Section A3–3.3.

A3–1.3 HEPATITIS B REACTIVATION

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in participants treated with anti-CD20 antibodies, including obinutuzumab in hematologic malignancies.

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

Guidelines for management of participants who develop hepatitis B reactivation are provided in Section A3–3.3.

A3–1.4 PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Progressive multifocal leukoencephalopathy (PML) has been reported in participants treated with obinutuzumab. The diagnosis of PML should be considered in any participants 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.

Participants should be referred to a neurologist for the evaluation and treatment of PML.

Guidelines for management of participants who develop PML are provided in Section A3–3.3.

A3–1.5 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 prohibited during the study and until B-cell recovery.

A3–1.6 DRUG-RELATED NEUTROPENIA

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

In NOBILITY study in participants with LN, as of the Week 104 data cutoff, drug-related neutropenia was seen in 3 participants (four events) in the in the obinutuzumab + MMF arm and in 2 participants (two events) in the placebo + MMF arm. Of the four neutropenia events in the obinutuzumab + MMF arm, two were Grade 4, one was Grade 3, and one was Grade 2. All events resolved, with two Grade 4 events requiring treatment with filgrastim. No additional drug-related neutropenia events were seen through the NOBILITY study's Week 104 data cut.

Guidelines for management of participants who develop neutropenia are provided in Section A3–3.3.

A3–1.7 DRUG-RELATED 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 participants treated with obinutuzumab for hematologic malignancy.

In the NOBILITY study, as of the Week 104 data cutoff, no events of study drug-related thrombocytopenia had been reported.

Guidelines for management of participants who develop thrombocytopenia are provided in Section A3–3.3.

A3–1.8 COAGULATION ABNORMALITIES INCLUDING DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

Coagulation abnormalities including DIC have been reported in adult patients receiving obinutuzumab for treatment of hematologic malignancies. In the majority of cases, the events have 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 (TLS). No specific baseline risk factors for DIC in patients treated with obinutuzumab have been identified.

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

A3–1.9 B-CELL DEPLETION AND RECOVERY

B-cell recovery has taken place whenever peripheral B cells are no longer depleted. B-cell peripheral blood depletion is defined as peripheral CD19+ count below the lower limit of quantification, defined as [redacted] B-cell recovery is defined as

peripheral CD19+ count at the participant's pretreatment baseline level or the lower limit of normal (LLN) for the population under study, whichever is lower.

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 [redacted]

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 the rituximab arm. The median level of CD19 cells was 0.079×10^9 cells/L at baseline and decreased rapidly to 0 cells/L by 2.5 hours post-infusion on Day 1 of Cycle 1. At the end of the treatment phase, of the patients with known B-cell status, 80 patients receiving rituximab (95%) and 82 patients receiving obinutuzumab (96%) had B-cell depletion. At 18 months post-treatment, 5 of 8 patients receiving rituximab and 17 of 19 patients receiving obinutuzumab (among those tested) 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 (86%) with available data had B-cell depletion at the end of treatment. Twenty-seven of these patients had at least 6 months of follow-up information (after the final 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 because they had progressed, 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.

A3–1.10 IMMUNOGLOBULIN DEPLETION AND RECOVERY

When obinutuzumab has been used for treatment of hematologic malignancies, immunoglobulin depletion and recovery has varied. In the Phase I Study BO20999 in

participants with NHL, the levels of IgA, IgG, and IgM were either low or normal for the duration of the treatment period. For participants 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 had returned to baseline levels 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 levels 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 populations or dose groups were observed in either treatment arm.

In the NOBILITY study, the proportion of participants with serum immunoglobulins levels below the LLN (LLN is 0.7 g/L, 5.65 g/L, and 0.4 g/L for IgA, IgG, and IgM, respectively) are provided in Table A3-1 for both treatment arms. The difference in the percentage of participants with values below LLN appears to be highest for IgM starting to show 3 months after initiation of treatment and being consistently 3- to 4-fold higher with 38% and 11% at Week 104 for the obinutuzumab and placebo arms respectively.

Guidelines for management of participants who develop hypogammaglobulinaemia are provided in Section A3–3.3.

Table A3-1 Percentage of Participants with IgG, IgA, and IgM Levels Less than LLN

	IgG (%)		IgA (%)		IgM (%)	
Visit	Placebo+MMF n=61	Obi+MMF n=64	Placebo+MMF n=61	Obi+MMF n=64	Placebo+MMF n=61	Obi+MMF n=64
Baseline	21.3	20.3	3.3	0	11.4	17.2
Week 12	18.3	23.0	5.0	1.6	13.3	36.1
Week 24	8.6	16.7	5.2	3.3	12.1	45.0
Week 52	1.8	11.5	1.8	3.3	10.5	41.0
Week 76	8.2	10.5	2.0	7.0	10.2	38.6
Week 104	4.3	8.9	2.2	8.9	10.9	37.5

LLN=lower limit of normal; MMF=mycophenolate mofetil; obi=obinutuzumab; n=number of participants.
Note: Below 0.7 g/L, 5.65 g/L, and 0.4 g/L for IgA, IgG, and IgM, respectively. Source: CSR WA29748.

A3–1.11 GASTROINTESTINAL PERFORATION

In the pivotal study in NHL, cases of gastrointestinal (GI) perforation have been reported in participants treated with obinutuzumab in association with bendamustine. Participants 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 in participants with LN, as of the Week 104 data cutoff, 1 participant (1.6%) in the placebo + MMF arm and 2 participants (3.1%) in the obinutuzumab + MMF arm experienced GI perforation. No additional GI perforation events were seen through the NOBILITY study's Week 104 data cut.

Guidelines for management of participants who develop gastrointestinal perforation are provided in Section A3–3.3.

A3–1.12 WORSENING OF PREEXISTING CARDIAC CONDITIONS

In participants 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, participants with a history of cardiac disease should be monitored closely. In addition, these participants 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.

Guidelines for management of participants who develop worsening of preexisting cardiac conditions are provided in Section A3–3.3.

A3–2 RISKS ASSOCIATED WITH MMF

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

A3–3 MANAGEMENT OF PARTICIPANTS WHO EXPERIENCE ADVERSE EVENTS

A3–3.1 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 participant experiences an IRR that requires interruption of the infusion and the investigator determines to permanently discontinue obinutuzumab infusions, the participant should continue to be followed in the study for safety.

See Section A10–2 or prescribing information for MMF dose modification guidance.

A3–3.2 TREATMENT INTERRUPTION

Obinutuzumab and MMF may be withheld in participants who experience toxicity considered to be related to study drug. Obinutuzumab and MMF may be withheld for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

A3–3.3 MANAGEMENT GUIDELINES

Guidelines for management of specific adverse events are outlined in Table A3-2. Additional guidelines are provided in the subsections below.

Table A3-2 Guidelines for Management of Participants Who Experience Adverse Events

Event	Action to Be Taken
IRR to obinutuzumab infusion	• Participants who have preexisting cardiac or pulmonary conditions should be monitored carefully throughout the infusion and the post-infusion period. • Withholding of anti-hypertensive treatments should be considered for 12 hours prior to and throughout each obinutuzumab infusion and for the first hour after administration. • Participants 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. • Participants with known IgE-mediated hypersensitivity to obinutuzumab or any component of the obinutuzumab infusion must not be treated. • Life-threatening (grade 4) IRR or recurrence of severe (grade 3) IRR upon re-challenge; for children below 12 years of age, therapy should be discontinued if an IRR is severe and deemed clinically serious (according to protocol-defined criteria for serious adverse events) or in the setting of escalation from moderate to severe IRR upon rechallenge. • *For additional guidance see Sections 7.1, A10–1 and Appendix 7*

Table A3-2 Guidelines for Management of Participants Who Experience Adverse Events (cont.)

Event	Action to Be Taken
Infections: general guidance	• No participant will be enrolled with a major active infection or history of chronic or recurring infections (excluding fungal infection of skin and/or nail beds). • Participants who develop an active infection during the study will have obinutuzumab infusions withheld until the event has resolved. • For all serious infectious adverse events reported, CBC with differential, quantitative immunoglobulins, and flow cytometry should be measured within 1 week of onset • Participants who require vaccination should be vaccinated at least 28 days prior to receiving obinutuzumab. • Vaccination with live vaccine through the end of study participation is contraindicated (see Section 6.8)
Infections: hepatitis B reactivation	• Hepatitis B screening is required prior to initiation of obinutuzumab. • Participants with active or chronic hepatitis B will be excluded from the study. • If HBV reactivation is observed: • Obinutuzumab infusions should be permanently discontinued (see Section 7.1). • Antiviral therapy must be started as per EASL 2017 Clinical Practice guidelines or local guidelines. • Referral to a hepatologist is recommended. • Participants will be monitored regularly for transaminases elevation. If transaminases elevation is observed, participants will be promptly referred to a hepatologist for evaluation and treatment.
Suspected PML	• Stop obinutuzumab infusions. • Obtain neurological consult. • In consultation with a neurologist, an MRI scan and lumbar puncture are recommended to assess for CSF JC viral DNA. • Notify monitors immediately.

Table A3-2 Guidelines for Management of Participants Who Experience Adverse Events (cont.)

Event	Action to Be Taken
Neutropenia	• Participants who experience neutropenia should be closely monitored with regular laboratory tests until resolution. • 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. • *Severe* or life-threatening neutropenia *(ANC below 1.0 x10³ cells/µL)* that does not resolve to *mild or moderate neutropenia (ANC higher than 1.5 x10³ cells/µL)* 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 in hematologic malignancy.
Thrombocytopenia	• Participants 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. • *For participants <12 years of age, platelet counts that remain below 110,000 cells/µL for longer than 8 weeks is a treatment discontinuation criterion. For participants < 12 years of age, platelet counts that remain below 50,000/µL for longer than 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.

Table A3-2 Guidelines for Management of Participants Who Experience Adverse Events (cont.)

Event	Action to Be Taken
Hypogammaglobulinemia	• Ig levels will be monitored throughout the study period. • IVIg should be considered for participants with recurrent/severe infections despite appropriate treatment, with concomitant hypogammaglobulinemia.
GI perforations	• Participants presenting with new-onset abdominal symptoms should be promptly evaluated.
Worsening of preexisting cardiac conditions	• Closely monitor participants with underlying cardiac conditions • Caution to be taken when hydrating participants with underlying cardiac conditions to prevent a potential fluid overload.

CSF = cerebrospinal fluid; EASL = European Association for the Study of the Liver; GI = gastrointestinal; RR = infusion-related reaction; IVIg = intravenous immunoglobulin; JC = John Cunningham; MRI = magnetic resonance imaging; PML = progressive multifocal leukoencephalopathy.

REFERENCES

Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med 2014;370:1101–10.

Appendix 4
Contraceptive and Barrier Guidance

Table of Contents

A4–1 Pregnancies in Female Participants 141
A4–2 Pregnancies in Female Partners of Male Participants 141
A4–3 Abortions 142
A4–4 Abnormal Pregnancy Outcomes 142

A4–1 PREGNANCIES IN FEMALE PARTICIPANTS

Female participants 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 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 the investigator becomes aware 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 treatment and counsel the participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant 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 or birth defect in the child) should be reported on the Adverse Event electronic Case Report Form (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.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A4–2 PREGNANCIES IN FEMALE PARTNERS OF MALE PARTICIPANTS

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if a female 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 participant exposed to study treatment. 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.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male participant 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.

A4–3 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 the investigator becomes aware of the event; see Section A2–5).

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 the investigator becomes aware of the event; see Section A2–5). 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.

A4–4 ABNORMAL PREGNANCY OUTCOMES

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomaly, birth defect, ectopic pregnancy) in a female participant exposed to study treatment or the female partner of a male participant exposed to study treatment 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 the investigator becomes aware of the event; see Section A2–5).

Appendix 5
Clinical Outcome Assessment Instruments

Table of Contents

A5–1 Clinical Outcome Assessment Instruments 144
A5–2 PedsQL Pediatric Quality of Life Inventory 145
A5–2.1 PedsQL Pediatric Quality of Life Inventory Parent Report for Toddlers (2–4) 145
A5–2.2 PedsQL Pediatric Quality of Life Inventory Parent Report for Young Children (5–7) 147
A5–2.3 PedsQL Pediatric Quality of Life Inventory Parent Report for Children (8–12) 149
A5–2.4 PedsQL Pediatric Quality of Life Inventory for Teens (13–18) 151
A5–2.5 PedsQL Pediatric Quality of Life Inventory Parent Report for Teens (13–18) 153
A5–2.6 PedsQL Quality of Life Inventory for Young Adults (18–25) 155
A5–3 PedsQL Multidimensional Fatigue Scale 157
A5–3.1 PedsQL Multidimensional Fatigue Scale Parent Report for Toddlers (2–4) 157
A5–3.2 PedsQL Multidimensional Fatigue Scale Parent Report for Young Children (5–7) 159
A5–3.3 PedsQL Multidimensional Fatigue Scale Parent Report for Children (8–12) 161
A5–3.4 PedsQL Multidimensional Fatigue Scale for Teens (13–18) 163
A5–3.5 PedsQL Multidimensional Fatigue Scale Parent Report for Teens (13–18) 165
A5–3.6 PedsQL Multidimensional Fatigue Scale for Young Adults (18–25) 167
A5–4 CureGN Edema Scale (English) 169
A5–5 Subject's Global Assessment 170
A5–6 Subject's Global Assessment (Parent Proxy) 172
A5–7 Physician's Global Assessment (English) 174
A5–8 SUPPLEMENTAL QUESTIONNAIRE FOR FATIGUE AND PHYSICAL FUNCTIONING (Patient Self Report Version) *175*
A5–9 SUPPLEMENTAL QUESTIONNAIRE FOR FATIGUE AND PHYSICAL FUNCTIONING (Parent/Caregiver Version) *178*

A5–1 CLINICAL OUTCOME ASSESSMENT INSTRUMENTS

PRO instruments will be self-administered at the clinic at specified timepoints during the study (see Schedule of Activities in Section 1.3). At the clinic, instruments will be administered before the participant or parent receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment.

The PRO instruments, translated into the local language as appropriate, will be provided by the Sponsor in pre-printed booklets to enable the appropriate instruments to be administered in the correct order at each specified timepoint.

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

- Participants' 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 participants to complete the instruments, estimated to be 20 minutes at each specified visit.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Participants/Parents 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.
- Participants/Parents 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 participants to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the participants 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 Section 1.3). ClinRO instruments will be self-administered.

A5–2 PEDSQL PEDIATRIC QUALITY OF LIFE INVENTORY

A5–2.1 PEDSQL PEDIATRIC QUALITY OF LIFE INVENTORY PARENT REPORT FOR TODDLERS (2–4)

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ID# _____

Date: _____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for **TODDLERS** (ages **2-4**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

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PedsQL-4.0-Core-PT - United States/English – Original version
PedsQL-4.0-Core-PT_AU4.0_eng-USon

PedsQL 2

*In the past **ONE month**, how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in active play or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Bathing	0	1	2	3	4
6. Helping to pick up his or her toys	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Playing with other children	0	1	2	3	4
2. Other kids not wanting to play with him or her	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

***Please complete this section if your child attends school or daycare**

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Doing the same school activities as peers	0	1	2	3	4
2. Missing school/daycare because of not feeling well	0	1	2	3	4
3. Missing school/daycare to go to the doctor or hospital	0	1	2	3	4

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A5–2.2 PEDSQL PEDIATRIC QUALITY OF LIFE INVENTORY PARENT REPORT FOR YOUNG CHILDREN (5–7)

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ID#_____

Date:_____

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Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for **YOUNG CHILDREN** (ages **5-7**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
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PedsQL 2

*In the past **ONE month,** how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores, like picking up his or her toys	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other children	0	1	2	3	4
2. Other kids not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with school activities	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

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A5–2.3 PEDSQL PEDIATRIC QUALITY OF LIFE INVENTORY PARENT REPORT FOR CHILDREN (8–12)

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Date: _____

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PARENT REPORT for **CHILDREN** (ages **8-12**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
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PedsQL 2

*In the past **ONE month,** how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other children	0	1	2	3	4
2. Other kids not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

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A5–2.4 PEDSQL PEDIATRIC QUALITY OF LIFE INVENTORY FOR TEENS (13–18)

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Pediatric Quality of Life Inventory

Version 4.0

TEEN REPORT (ages **13-18**)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

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PedsQL 2

*In the past **ONE month**, how much of a **problem** has this been for you …*

ABOUT MY HEALTH AND ACTIVITIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

ABOUT MY FEELINGS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

HOW I GET ALONG WITH OTHERS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other teens	0	1	2	3	4
2. Other teens do not want to be my friend	0	1	2	3	4
3. Other teens tease me	0	1	2	3	4
4. I cannot do things that other teens my age can do	0	1	2	3	4
5. It is hard to keep up with my peers	0	1	2	3	4

ABOUT SCHOOL *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

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A5–2.5 PEDSQL PEDIATRIC QUALITY OF LIFE INVENTORY PARENT REPORT FOR TEENS (13–18)

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Pediatric Quality of Life Inventory

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PARENT REPORT for **TEENS** (ages **13-18**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your teen**. Please tell us **how much of a problem** each one has been for **your teen** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

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PedsQL 2

*In the past **ONE month,** how much of a **problem** has your teen had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other teens	0	1	2	3	4
2. Other teens not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other teens	0	1	2	3	4
4. Not able to do things that other teens his or her age can do	0	1	2	3	4
5. Keeping up with other teens	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

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A5–2.6 PEDSQL QUALITY OF LIFE INVENTORY FOR YOUNG ADULTS (18–25)

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Young Adult Quality of Life Inventory

Version 4.0

YOUNG ADULT REPORT (ages **18-25**)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

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PedsQL 2

*In the past **ONE month**, how much of a **problem** has this been for you …*

ABOUT MY HEALTH AND ACTIVITIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

ABOUT MY FEELINGS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

HOW I GET ALONG WITH OTHERS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other young adults	0	1	2	3	4
2. Other young adults do not want to be my friend	0	1	2	3	4
3. Other young adults tease me	0	1	2	3	4
4. I cannot do things that others my age can do	0	1	2	3	4
5. It is hard to keep up with my peers	0	1	2	3	4

ABOUT MY WORK/STUDIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention at work or school	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my work or studies	0	1	2	3	4
4. I miss work or school because of not feeling well	0	1	2	3	4
5. I miss work or school to go to the doctor or hospital	0	1	2	3	4

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A5–3 PEDSQL MULTIDIMENSIONAL FATIGUE SCALE

A5–3.1 PEDSQL MULTIDIMENSIONAL FATIGUE SCALE PARENT REPORT FOR TODDLERS (2–4)

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Multidimensional Fatigue Scale

Version 3.0

PARENT REPORT for **TODDLERS** (ages **2-4**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

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PedsQL 2

*In the past **ONE month,** how much of a **problem** has this been for your child …*

GENERAL FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling tired	0	1	2	3	4
2. Feeling physically weak (not strong)	0	1	2	3	4
3. Feeling too tired to do things that he/she likes to do	0	1	2	3	4
4. Feeling too tired to spend time with his/her friends	0	1	2	3	4
5. Trouble finishing things	0	1	2	3	4
6. Trouble starting things	0	1	2	3	4

SLEEP/REST FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Sleeping a lot	0	1	2	3	4
2. Difficulty sleeping through the night	0	1	2	3	4
3. Feeling tired when he/she wakes up in the morning	0	1	2	3	4
4. Resting a lot	0	1	2	3	4
5. Taking a lot of naps	0	1	2	3	4
6. Spending a lot of time in bed	0	1	2	3	4

COGNITIVE FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Difficulty keeping his/her attention on things	0	1	2	3	4
2. Difficulty remembering what people tell him/her	0	1	2	3	4
3. Difficulty remembering what he/she just heard	0	1	2	3	4
4. Difficulty thinking quickly	0	1	2	3	4
5. Trouble remembering what he/she was just thinking	0	1	2	3	4
6. Trouble remembering more than one thing at a time	0	1	2	3	4

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A5–3.2 PEDSQL MULTIDIMENSIONAL FATIGUE SCALE PARENT REPORT FOR YOUNG CHILDREN (5–7)

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Multidimensional Fatigue Scale

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PARENT REPORT for **YOUNG CHILDREN** (ages **5-7**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

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PedsQL 2

*In the past **ONE month,** how much of a **problem** has this been for your child …*

GENERAL FATIGUE *(PROBLEMS WITH…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling tired	0	1	2	3	4
2. Feeling physically weak (not strong)	0	1	2	3	4
3. Feeling too tired to do things that he/she likes to do	0	1	2	3	4
4. Feeling too tired to spend time with his/her friends	0	1	2	3	4
5. Trouble finishing things	0	1	2	3	4
6. Trouble starting things	0	1	2	3	4

SLEEP/REST FATIGUE *(PROBLEMS WITH…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Sleeping a lot	0	1	2	3	4
2. Difficulty sleeping through the night	0	1	2	3	4
3. Feeling tired when he/she wakes up in the morning	0	1	2	3	4
4. Resting a lot	0	1	2	3	4
5. Taking a lot of naps	0	1	2	3	4
6. Spending a lot of time in bed	0	1	2	3	4

COGNITIVE FATIGUE *(PROBLEMS WITH…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Difficulty keeping his/her attention on things	0	1	2	3	4
2. Difficulty remembering what people tell him/her	0	1	2	3	4
3. Difficulty remembering what he/she just heard	0	1	2	3	4
4. Difficulty thinking quickly	0	1	2	3	4
5. Trouble remembering what he/she was just thinking	0	1	2	3	4
6. Trouble remembering more than one thing at a time	0	1	2	3	4

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A5–3.3 PEDSQL MULTIDIMENSIONAL FATIGUE SCALE PARENT REPORT FOR CHILDREN (8–12)

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PARENT REPORT for **CHILDREN** (ages **8-12**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

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PedsQL 2

*In the past **ONE month,** how much of a **problem** has this been for your child …*

GENERAL FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling tired	0	1	2	3	4
2. Feeling physically weak (not strong)	0	1	2	3	4
3. Feeling too tired to do things that he/she likes to do	0	1	2	3	4
4. Feeling too tired to spend time with his/her friends	0	1	2	3	4
5. Trouble finishing things	0	1	2	3	4
6. Trouble starting things	0	1	2	3	4

SLEEP/REST FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Sleeping a lot	0	1	2	3	4
2. Difficulty sleeping through the night	0	1	2	3	4
3. Feeling tired when he/she wakes up in the morning	0	1	2	3	4
4. Resting a lot	0	1	2	3	4
5. Taking a lot of naps	0	1	2	3	4
6. Spending a lot of time in bed	0	1	2	3	4

COGNITIVE FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Difficulty keeping his/her attention on things	0	1	2	3	4
2. Difficulty remembering what people tell him/her	0	1	2	3	4
3. Difficulty remembering what he/she just heard	0	1	2	3	4
4. Difficulty thinking quickly	0	1	2	3	4
5. Trouble remembering what he/she was just thinking	0	1	2	3	4
6. Trouble remembering more than one thing at a time	0	1	2	3	4

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A5–3.4 PEDSQL MULTIDIMENSIONAL FATIGUE SCALE FOR TEENS (13–18)

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TEEN REPORT (ages **13-18**)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

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PedsQL 2

*In the past **ONE month,** how much of a **problem** has this been for you …*

GENERAL FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel tired	0	1	2	3	4
2. I feel physically weak (not strong)	0	1	2	3	4
3. I feel too tired to do things that I like to do	0	1	2	3	4
4. I feel too tired to spend time with my friends	0	1	2	3	4
5. I have trouble finishing things	0	1	2	3	4
6. I have trouble starting things	0	1	2	3	4

SLEEP/REST FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I sleep a lot	0	1	2	3	4
2. It is hard for me to sleep through the night	0	1	2	3	4
3. I feel tired when I wake up in the morning	0	1	2	3	4
4. I rest a lot	0	1	2	3	4
5. I take a lot of naps	0	1	2	3	4
6. I spend a lot of time in bed	0	1	2	3	4

COGNITIVE FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to keep my attention on things	0	1	2	3	4
2. It is hard for me to remember what people tell me	0	1	2	3	4
3. It is hard for me to remember what I just heard	0	1	2	3	4
4. It is hard for me to think quickly	0	1	2	3	4
5. I have trouble remembering what I was just thinking	0	1	2	3	4
6. I have trouble remembering more than one thing at a time	0	1	2	3	4

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A5–3.5 PEDSQL MULTIDIMENSIONAL FATIGUE SCALE PARENT REPORT FOR TEENS (13–18)

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PARENT REPORT for **TEENS** (ages **13-18**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

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PedsQL 2

*In the past **ONE month,** how much of a **problem** has this been for your child …*

GENERAL FATIGUE ***(problems with…)***	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling tired	0	1	2	3	4
2. Feeling physically weak (not strong)	0	1	2	3	4
3. Feeling too tired to do things that he/she likes to do	0	1	2	3	4
4. Feeling too tired to spend time with his/her friends	0	1	2	3	4
5. Trouble finishing things	0	1	2	3	4
6. Trouble starting things	0	1	2	3	4

SLEEP/REST FATIGUE ***(problems with…)***	Never	Almost Never	Some-times	Often	Almost Always
1. Sleeping a lot	0	1	2	3	4
2. Difficulty sleeping through the night	0	1	2	3	4
3. Feeling tired when he/she wakes up in the morning	0	1	2	3	4
4. Resting a lot	0	1	2	3	4
5. Taking a lot of naps	0	1	2	3	4
6. Spending a lot of time in bed	0	1	2	3	4

COGNITIVE FATIGUE ***(problems with…)***	Never	Almost Never	Some-times	Often	Almost Always
1. Difficulty keeping his/her attention on things	0	1	2	3	4
2. Difficulty remembering what people tell him/her	0	1	2	3	4
3. Difficulty remembering what he/she just heard	0	1	2	3	4
4. Difficulty thinking quickly	0	1	2	3	4
5. Trouble remembering what he/she was just thinking	0	1	2	3	4
6. Trouble remembering more than one thing at a time	0	1	2	3	4

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PedsQL-3.0-Fatigue PA - United States/English - Mapi.
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A5–3.6 PEDSQL MULTIDIMENSIONAL FATIGUE SCALE FOR YOUNG ADULTS (18–25)

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

ID#_____

Date:_____

PedsQL™

Multidimensional Fatigue Scale

Version 3.0

YOUNG ADULT REPORT (ages **18-25**)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

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PedsQL-3.0-Fatigue Yad - United States/English - Mapi.
PedsQL-3.0Fatigue-Yad_AU3.0_eng-USori.doc

PedsQL 2

*In the past **ONE month,** how much of a **problem** has this been for you …*

GENERAL FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel tired	0	1	2	3	4
2. I feel physically weak (not strong)	0	1	2	3	4
3. I feel too tired to do things that I like to do	0	1	2	3	4
4. I feel too tired to spend time with my friends	0	1	2	3	4
5. I have trouble finishing things	0	1	2	3	4
6. I have trouble starting things	0	1	2	3	4

SLEEP/REST FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I sleep a lot	0	1	2	3	4
2. It is hard for me to sleep through the night	0	1	2	3	4
3. I feel tired when I wake up in the morning	0	1	2	3	4
4. I rest a lot	0	1	2	3	4
5. I take a lot of naps	0	1	2	3	4
6. I spend a lot of time in bed	0	1	2	3	4

COGNITIVE FATIGUE *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to keep my attention on things	0	1	2	3	4
2. It is hard for me to remember what people tell me	0	1	2	3	4
3. It is hard for me to remember what I just heard	0	1	2	3	4
4. It is hard for me to think quickly	0	1	2	3	4
5. I have trouble remembering what I was just thinking	0	1	2	3	4
6. I have trouble remembering more than one thing at a time	0	1	2	3	4

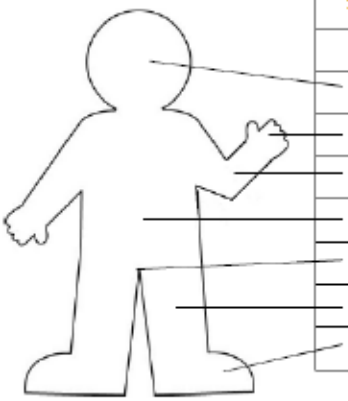
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A5–4 CUREGN EDEMA SCALE (ENGLISH)

Study Number: WA43380 Site Number:	Subject Number: Date of Assessment:	Visit Name: Week: ☐☐

For each body location, please list the severity of any swelling you have **experienced over the last month**. Please rate the severity using the scale below, where a score of zero indicates an absence of swelling and a score of five indicates the worst imaginable swelling in a specific body location. Please complete the rating for each body location indicated below.



	Absent					Worst Imaginable
1. Swelling in your:						
a. Whole body	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Face or around your eyes	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Fingers or hands	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Arms	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Stomach or abdomen	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Genitalia	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Legs	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Feet	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

A5–5 SUBJECT'S GLOBAL ASSESSMENT

Use the original document provided by sponsor.

Do not photocopy the document since this may alter the length of the 100 mm line.

Protocol WA43380

English (United States)

SUBJECT'S GLOBAL ASSESSMENT

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 illness affects you, where would you rate your current 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

Respondent Initials: _____ Date:_____

A5–6 SUBJECT'S GLOBAL ASSESSMENT (PARENT PROXY)

Use the original document provided by sponsor.

Do not photocopy the document since this may alter the length of the 100 mm line.

Protocol WA43380

English (United States)

SUBJECT'S GLOBAL ASSESSMENT

(Parent Proxy)

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 child's illness affects them, where would you rate your child's current 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

Respondent Initials: _____ Date:_____

A5–7 PHYSICIAN'S GLOBAL ASSESSMENT (ENGLISH)

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

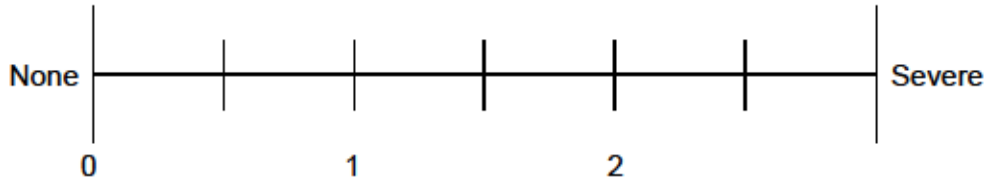
Check if assessment was not done: ☐

Date of Assessment: __ __ - __ __ - __ __ __
d d m m y y y

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 nephrotic syndrome since the patient started taking the study drug?



_____ mm

A5–8 SUPPLEMENTAL QUESTIONNAIRE FOR FATIGUE AND PHYSICAL FUNCTIONING (PATIENT SELF REPORT VERSION)

Use the original document provided by sponsor.
Do not photocopy the document.

Protocol WA43380

English (United States)

Supplemental Questionnaire for Fatigue and Physical Functioning

(Patient Self-Report Version)

We would like to understand a bit more about your experience of fatigue and any changes in physical functioning due to Nephrotic Syndrome. Please complete the following questions. There are no right or wrong answers.

GENERAL FATIGUE

The first two questions ask about your general fatigue during the course of this clinical trial. "General fatigue" includes: feeling tired or physically weak, feeling too tired to do the things you enjoy, like being with friends, or having trouble finishing things or starting things.

When compared to the beginning of this clinical trial, how would you rate your current general fatigue level over the last ONE month? Please choose only one that applies.

I have much less fatigue now compared to the beginning of this clinical trial.	☐
I have somewhat less fatigue now compared to the beginning of this clinical trial.	☐
I have the same amount of fatigue now compared to the beginning of this clinical trial.	☐
I have somewhat more fatigue now compared to the beginning of this clinical trial.	☐
I have much more fatigue now compared to the beginning of this clinical trial.	☐

When compared to the beginning of this clinical trial, do you feel you have had a meaningful improvement in your general fatigue level?

Yes ☐

No ☐

PHYSICAL FUNCTIONING

***The final two questions ask about your physical functioning** during the course of this clinical trial. "Physical functioning" reflects how able you are to do things such as: walking, running, participating in exercise, bathing, doing chores at home; or how unable you are to do these activities because you experience body aches and pains.*

When compared to the beginning of this clinical trial, how would you rate your current physical functioning over the last ONE month? Please choose only one that applies.

*My physical functioning is **much better** now compared to the beginning of this clinical trial.*	☐
*My physical functioning is **somewhat better** now compared to the beginning of this clinical trial.*	☐
*My physical functioning is **the same** now compared to the beginning of this clinical trial.*	☐
*My physical functioning is **somewhat worse** now compared to the beginning of this clinical trial.*	☐
*My physical functioning is **much worse** now compared to the beginning of this clinical trial.*	☐

When compared to the beginning of this clinical trial, do you feel you have had a meaningful improvement in your physical functioning?

Yes ☐
No ☐

Thank you for completing this questionnaire.

A5–9 SUPPLEMENTAL QUESTIONNAIRE FOR FATIGUE AND PHYSICAL FUNCTIONING (PARENT/CAREGIVER VERSION)

Use the original document provided by sponsor.
Do not photocopy the document.

Protocol WA43380

English (United States)

Supplemental Questionnaire for Fatigue and Physical Functioning

(Parent/Caregiver Version)

We would like to understand a bit more about your child's experience of fatigue and any changes in physical functioning due to Nephrotic Syndrome. Please complete the following questions. There are no right or wrong answers.

GENERAL FATIGUE

The first two questions ask about your child's general fatigue during the course of this clinical trial. "General fatigue" includes: feeling tired or physically weak, feeling too tired to do the things he/she enjoys, like being with friends, or having trouble finishing things or starting things.

When compared to the beginning of this clinical trial, how would you rate your child's current general fatigue level over the last ONE month? Please choose only one that applies.

They have much less fatigue now compared to the beginning of this clinical trial.	☐
They have somewhat less fatigue now compared to the beginning of this clinical trial.	☐
They have the same amount of fatigue now compared to the beginning of this clinical trial.	☐
They have somewhat more fatigue now compared to the beginning of this clinical trial.	☐
They have much more fatigue now compared to the beginning of this clinical trial.	☐

When compared to the beginning of this clinical trial, do you feel your child has had a meaningful improvement in their general fatigue level?

Yes ☐

No ☐

PHYSICAL FUNCTIONING

The final two questions ask about your child's physical functioning *during the course of this clinical trial. "Physical functioning" reflects how able they are to do things such as: walking, running, participating in exercise, bathing, doing chores at home; or how unable they are to do these activities because they experience body aches and pains.*

When compared to the beginning of this clinical trial, how would you rate your child's current physical functioning over the last ONE month? Please choose only one that applies.

*Their physical functioning is **much better** now compared to the beginning of this clinical trial.*	☐
*Their physical functioning is **somewhat better** now compared to the beginning of this clinical trial.*	☐
*Their physical functioning is **the same** now compared to the beginning of this clinical trial.*	☐
*Their physical functioning is **somewhat worse** now compared to the beginning of this clinical trial.*	☐
*Their physical functioning is **much worse** now compared to the beginning of this clinical trial.*	☐

When compared to the beginning of this clinical trial, do you feel your child has had a meaningful improvement in their physical functioning?

Yes ☐
No ☐

Thank you for completing this questionnaire.

Appendix 6 Clinical Safety Laboratory Tests

With the exception of urine pregnancy tests or if otherwise noted, the tests detailed in Table A6-1 will be performed by the central laboratory.

In general, local laboratory tests should not be used unless specified in Table 1 or Table A6-1. However, if local laboratory results are inadvertently used to make either a study treatment decision or a response evaluation, the results, together with the local laboratory reference ranges for the parameter being assessed, must be entered on the electronic Case Report Form. It is important that a sample for central analysis is obtained at the same time.

Protocol-specific requirements for inclusion and exclusion of participants are detailed in Section 5.

Additional tests may be performed at any time during the study if determined to be necessary by the investigator or if required by local regulations.

Table A6-1 Protocol-Required Safety Laboratory Assessments

Central Laboratory Tests
• Hematology: CBC, WBC count, RBC count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and quantitative platelet count, and differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells). • Chemistry panel (serum or plasma): albumin, alkaline phosphatase, ALT, AST, Bicarbonate, Calcium, Chloride, Cholesterol, Creatinine, Creatinine Kinase, Direct Bilirubin, GGT, globulin, random Glucose, Indirect Bilirubin, lactate dehydrogenase Magnesium, Phosphorus, Potassium, Sodium, Total Bilirubin, Total Protein, Triglycerides, Urea Nitrogen, Uric Acid. • HIV serology: HIV-1 antibody/HIV-1/2 antibody/HIV-2 antibody [a] • *TB testing* [b] • HBV serology: HBsAg, HBsAb, and total HBcAb for all individuals • HCV serology: HCV antibody for all individuals • Quantitative immunoglobulins: IgA, IgG, and IgM • Pregnancy test – Females of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. Urine pregnancy tests will be performed locally at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Study drug infusions should not be administered unless the serum pregnancy test is negative. • Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, and blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria) • [redacted] • Urine pregnancy test on study treatment days

HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; [redacted]; LDH = lactate dehydrogenase; [redacted]
GGT = gamma-glutamyl transferase.

[a] For participants with unknown HIV status, HIV testing may be performed at screening only if required by local regulations

[b] *TB testing may be performed during screening only if required by local regulations*

Investigators must document their review of each laboratory safety report.

Appendix 7
Anaphylaxis Precautions

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

ANAPHYLAXIS DEFINITION CRITERIA

Anaphylaxis is highly likely when any one of the following 3 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, and 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 participant (minutes to several hours):
  - Involvement of the skin-mucosal tissue (e.g., generalized hives, itch, flush, swollen lips, tongue, and 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 participant (minutes to several hours):
  - Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP[1]

[1] Low systolic blood pressure for children is defined as less than 70 mm Hg for infants from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1–10 years, and less than 90 mm Hg in children from 11–17 years old.

REQUIRED EQUIPMENT AND MEDICATION

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

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intramuscular (preferred route), subcutaneous, intravenous, 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 administration, the following procedures should be performed:

1. Stop the study treatment administration, if possible.
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 participant status and as directed by the physician in charge.
6. Continue to observe the participant and document observations.

REFERENCES

Sampson HA, Muñoz-Furlong A, Campbell R, 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;117:391–97.

Appendix 8
Instructions for Collecting Urine Samples at Study Visits

For all visits requiring a central laboratory UPCR assessment (screening, Week 12, Week 24, Week 40, Week 52, Week 76 and early withdrawal) a first-morning void (FMV) urine sample is required. If a FMV urine sample cannot be collected, participants must provide a first-morning urine sample for analysis on a subsequent day, up to 2 weeks after the clinic visit. A 30-mL aliquot will be taken from this sample.

For confirmation of relapse, FMV urine is strongly preferred but a spot urine sample obtained subsequent to FMV (if unavailable) on the day of relapse, is permitted. The rationale for allowing urine samples subsequent to FMV to be utilized in this situation is that patients may require immediate initiation of systemic steroids/immunosuppressive agents for the treatment of relapse that would make analysis of FMV urine samples on subsequent days inaccurate as an assessment of relapse.

Written instructions should be given to the participant about how to collect a morning urine sample. In addition, it is encouraged to remind the participant that strenuous physical exercise should be avoided for the 72 hours preceding a urine collection and, in this case, first morning void is strongly preferred.

For patients with fever or signs/symptoms of infection, the Week 52 and/or Week 76 visit should be deferred for up to 2 weeks until fever and signs/symptoms of infection have resolved.

In females, urine collection should be avoided during menstruation.

THE 30-ML ALIQUOT FIRST MORNING VOID URINE SAMPLE

Thirty milliliters is the recommended volume and 18 mL is the minimum necessary volume.

The sample should be split into two equal parts:

- Central laboratory macroscopic and microscopic urinalysis
- Central laboratory urinary protein-to-creatinine ratio

Additional urine microscopic and macroscopic analyses may be performed on a separate aliquot from the FMV urine sample using standard methods if desired.

Appendix 9
Instructions for Collecting Urine Samples at Home

HOME URINE DIPSTICK ANALYSIS AND RELAPSE REPORTING

Urine protein determinations will be made using home urine dipsticks that will be provided to the family of each study participant. First morning (AM) urine will be collected in clean urine collection cups on a daily basis throughout the study. The urine dipstick will be briefly placed into the urine and readings made by the study participant's parent or caregiver (or participant themselves if appropriate) after approximately 60 seconds. The results must be recorded in the participant's daily logbook.

If a urine dipstick reading is ≥3+ (a reading of 3+ or higher) proteinuria, the remaining urine in the cup will be placed in the refrigerator in a plastic bag and labeled with the date of collection.

If the patient has edema at the time of urinalysis dipstick ≥3+, the patient will have met criteria for relapse regardless of the number of days of dipstick-assessed proteinuria. In such cases, the remaining urine will be collected from the patient and sent to the central laboratory for urine protein/creatinine ratio determination, with the precise date/time of collection of the sample.

If no edema is present and three consecutive first-AM urine samples confirm ≥3+ proteinuria by dipsticks, the patient will be declared in relapse, and the remaining urine from the most recent available day (e.g., the third day) will be sent to the central laboratory for urine protein/creatinine ratio determination, with the precise date/time of collection of the sample.

Refrigerated samples that are followed by urine samples with <3+ (less than 3+, for example a reading of 'negative', 'trace', 1+ or 2+) proteinuria and thus do not define a relapse will be discarded. **Prior to enrollment, the participant and family will be carefully instructed regarding the proper technique for home urine sample collections, dipstick analyses, urine cup date labeling and refrigeration steps, and recording results in the participant's logbook**. Successful completion of training will be documented prior to provision of the first dose of study drug for all participants.

Typical dipstick results are expressed semi-quantitatively as follows, or as stated by manufacturer:

Negative: 0 to <15mg/dL

Trace: 15 to <30mg/dL

1+: 30 to <100mg/dL

2+: 100 to <300mg/dL

3+: 300 to <1000mg/dL

4+: ≥1000mg/dL

Appendix 10
Obinutuzumab Dosing Schedule and Guidelines

Table of Contents

A10–1 Administration of Study Drug 188
A10–1.1 First Infusion (Day 1) 189
A10–1.2 Subsequent Infusions 191
A10–2 Guidelines for Mycophenolate Mofetil Dosing 194
A10–2.1 Target Dosing 194
A10–2.2 Escalation of Dose 194
A10–2.3 Adjustments to MMF Dose 194

A10–1 ADMINISTRATION OF STUDY DRUG

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

- Administration of obinutuzumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 7.
- Obinutuzumab infusions will be administered per the instructions outlined in Table A10-1. The guidelines below may be slowed at the discretion of the investigator based on a participant's clinical presentation.

Table A10-1 Administration of First and Subsequent Infusions of Obinutuzumab

First Infusion	Subsequent Infusions
• Begin infusion at an initial rate of *12.5 mL*/hr. • If no infusion-related or hypersensitivity reaction occurs, increase the infusion rate in *12.5 mL*/hr increments every 30 minutes, to a maximum of *100 mL*/hr. • If a reaction develops, stop or slow the infusion according to the Infusion Rate Modification Guidelines for Infusion-Related Reactions per Table A10-3. Administer medications and give supportive care in accordance with institutional guidelines. • If the reaction resolves, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time that the reaction occurred).	• If the participant experienced an infusion related- or hypersensitivity reaction during the prior infusion, begin infusion at an initial rate of *12.5 mL*/hr and follow instructions for first infusion. • If the participant tolerated the prior infusion well (defined by an absence of Grade 2 reactions during a final infusion rate of 100 *mL*/hr), begin infusion at a rate of *25 mL*/hr. • If no reaction occurs, increase the infusion rate in *25 mL*/hr increments every 30 minutes, to a maximum of *100 mL*/hr. • If a reaction develops, stop or slow the infusion as detailed by guidelines in Table A10-3. Administer medications and give supportive care in accordance with institutional guidelines. If the reaction resolves, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time that the reaction occurred).

Guidelines for medical management of infusion-related reactions (IRRs) are provided in the Appendix 3.

A10–1.1 FIRST INFUSION (DAY 1)

[redacted] The administration of all pre-medications must be completed between 30 and 60 minutes prior to the obinutuzumab infusion.

Note: Participants 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 *12.5 mL*/hr. This may be escalated at a rate of *12.5 mL*/hr every 30 minutes to a maximum of *100 mL*/hr. Table A10-2 presents the schedule for the first infusion.

Table A10-2 Schedule for First Infusion

The total dose of obinutuzumab administered will depend on weight. Participants with a body weight of 45 kg or more will receive a flat 1000-mg dose, whereas participants with a body weight below 45 kg will receive a weight-adjusted dose of 20 mg/kg with the same infusion rate. The same volume of 250 mL will be used to infuse all doses of obinutuzumab, regardless of participant body weight.

Schedule for the first obinutuzumab infusion in a participant weighing 45 kg or more:

	Infusion Rate	*Body weight = 45 kg or more*		
Time (min)	*(mL/hr)*	*Dose per interval (mg)*	*Cumulative Dose (mg)*	*Volume per interval*
0–30	*12.5*	*25*	*25*	*6.25*
31–60	*25*	*50*	*75*	*12.5*
61–90	*37.5*	*75*	*150*	*18.75*
91–120	*50*	*100*	*250*	*25*
121–150	*62.5*	*125*	*375*	*31.25*
151–180	*75*	*150*	*525*	*37.5*
181–210	*87.5*	*175*	*700*	*43.75*
211–240	*100*	*200*	*900*	*50*
241–255 [a]	*100*	*200*	*1000*	*25*

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

Appendix 10: Obinutuzumab Dosing Schedule and Guidelines

Example Schedule for the first obinutuzumab infusion in a participant weighing 20 kg:

	Infusion Rate	*Body weight = 20 kg*		
Time (min)	*(mL/hr)*	*Dose per interval (mg)*	*Cumulative Dose (mg)*	*Volume per interval*
0–30	*12.5*	*10*	*10*	*6.25*
31–60	*25*	*20*	*30*	*12.5*
61–90	*37.5*	*30*	*60*	*18.75*
91–120	*50*	*40*	*100*	*25*
121–150	*62.5*	*50*	*150*	*31.25*
151–180	*75*	*60*	*210*	*37.5*
181–210	*87.5*	*70*	*280*	*43.75*
211–240	*100*	*80*	*360*	*50*
241–255 [a]	*100*	*40*	*400*	*25*

[a] *Should complete at 225 minutes (4 hours, 15 minutes) to complete total dose.*

In the event that the participant experiences an IRR, see Table A10-3 below for infusion rate modification guidelines.

Table A10-3 Infusion Rate Modification Guidelines for Infusion-Related Reactions

AE CTC Grade	Modification Guidelines/Action
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 A10-2 and Table A10-4). • If the participant experiences a second occurrence of a Grade 3 IRR, stop infusion and permanently discontinue therapy. • *For children below 12 years of age, therapy should be discontinued if an IRR is severe and deemed clinically serious, according to protocol-defined criteria for serious adverse events* • *For children below 12 years of age, therapy should be discontinued in the setting of escalation from moderate to severe IRR upon rechallenge*
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 *mL*/hr to 50 *mL*/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 A10-2 and Table A10-4).

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.

A10–1.2 SUBSEQUENT INFUSIONS

[redacted]

[redacted] The administration of all premedications must be completed between 30 and 60 minutes prior to the obinutuzumab infusion.

Participants who tolerated the first infusion of obinutuzumab may receive the second infusion as detailed in see Table A10-4. Participants 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 $>50\ mL$/hr, then the second infusion rate should start at $12.5\ mL$/hr.

Infusions should be made through a dedicated line and commence at a rate of $25\ mL$/hr. This may be escalated at a rate of $25\ mL$/hr every 30 minutes to a maximum of $100\ mL$/hr. Table A10-4 presents the schedule for the second and subsequent infusions.

In the event that the participant experiences an IRR, refer to Table A10-3 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 A10-4 Schedule for Second and Subsequent Infusions

Infusion rates (mL/hr) will be the same for all participants receiving Obinutuzumab. The total dose of obinutuzumab administered will depend on weight. Participants with a body weight of 45 kg or more will receive a flat 1000-mg dose, whereas participants with a body weight below 45 kg will receive a weight-adjusted dose of 20 mg/kg with the same infusion rate. The same volume of 250 mL will be used to infuse all doses of obinutuzumab, regardless of participant body weight.

Schedule for the second and subsequent obinutuzumab infusions in a participant weighing 45 kg or more:

	Infusion Rate	Body weight 45 kg or more		
Time (min)	(mL/hr)	Dose per interval (mg)	Cumulative Dose (mg)	Volume per interval
0–30	25	50	50	12.5
31–60	50	100	150	25
61–90	75	150	300	37.5
91–120	100	200	500	50
121–150	100	200	700	50
151–180	100	200	900	50
181–195[a]	100	200	1000	25

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

Example schedule for the second and subsequent obinutuzumab infusions in a participant weighing 20 kg (dose of obintuzumab= 400 mg):

	Infusion Rate	Body weight= 20 kg		
Time (min)	(mL/hr)	Dose per interval (mg)	Cumulative Dose (mg)	Volume per interval
0–30	25	20	20	12.5
31–60	50	40	60	25
61–90	75	60	120	37.5
91–120	100	80	200	50
121–150	100	80	280	50
151–180	100	80	360	50
181–210[a]	100	40	400	25

[a] *Should complete at 195 minutes (3 hours, 15 minutes) to complete total dose*

A10–2 GUIDELINES FOR MYCOPHENOLATE MOFETIL DOSING

A10–2.1 TARGET DOSING

The target mycophenolate mofetil (MMF) dosage for the protocol is body surface area (BSA)-based at 1200 mg/m^2/day and is limited to a maximum daily dose of 2 grams outside of a relapse event. In Asia, lower MMF doses are permitted per local treatment guidelines.

Initial Dosing

Participants who enter the study and are naïve to MMF should be initiated on MMF below the target dose in divided doses, and reach the target dose of 1200 mg/m^2/day (maximum 2 g/day in divided doses) within 4 weeks of initiation.

Participants already receiving MMF prior to study entry should be titrated to the target dose of 1200 mg/m^2/day in divided doses by Day 1.

A10–2.2 ESCALATION OF DOSE

The dosage of MMF should be increased, as tolerated with the goal of reaching the target dose, in divided doses, by Week 4 at the latest. Up-titration to the target dose within 4 weeks will be performed according to local MMF treatment guidelines for the age and weight of the participant recognizing that BSA may be as low as 0.5 m^2 for younger pediatric participants.

A10–2.3 ADJUSTMENTS TO MMF DOSE

Investigators will be allowed to adjust the MMF dosage because of tolerance and adverse effects but the dosage should not be increased to greater than 2 g/day, unless to treat a relapse event. For a relapse event, the maximum dosage of MMF will be 2.5 g/day or 1200 mg/m^2/day, whichever is lower.

Participants who are newly initiating MMF at study onset will return at Week 2 for a scheduled study visit to include monitoring of CBC, liver function tests, and serum creatinine. Any patient who has not achieved the target dosage of MMF on or before Week 3 will return 1–2 weeks after the target dosage is achieved to obtain a local CBC for standard surveillance and monitoring. Thus, for patients who achieve the target dose by Week 4 but not before Week 3, such patients will have a local CBC assessed by the investigator between Weeks 5 and 6. It is also anticipated that, among patients initiating MMF at study onset, many such patients will have achieved the target dose of MMF on or before Week 3.

Some patients may enter the study on stable doses of MMF, and in such cases where MMF dosing was stable for at least 1 week prior to Day 1, it will not be necessary for

such patients to return for a Week 2 visit. All participants who are receiving MMF will return at Week 4 for monitoring of CBC, liver function tests, and serum creatinine, followed by monitoring every 2–3 months thereafter, which is considered sufficient for the surveillance of MMF-related toxicity.

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 A10-5.

If a participants develops GI toxicity due to MMF, it is recommended to reduce the dose according to "Step 1" as listed in Table A10-5 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 A10-5. After the symptoms resolve, an attempt should be made to increase MMF to a goal of 1200 mg/m^2/day per the previous dosing algorithm. If GI symptoms return, then the participant 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., *Clostridium difficile* and enteropathogens) should be ruled out and treated if necessary at the discretion of the investigator as per local clinical practice.

If a participant develops an absolute neutrophil count (ANC) between 1000 and 1200, the dose should be reduced according to "Step 1," as listed in Table A10-5 and the neutrophil count should be checked again at the next scheduled visit. If the ANC continues to be between 1000 and 1200 unit, the dose should be reduced according to "Step 2," as listed in Table A10-5. After the ANC increases to >1200 unit, the dose should be titrated towards goal, but at a rate of 500 mg per month.

If the participant's ANC is <1000 unit, MMF must be stopped immediately.
The participant must return within 14–21 days for repeat measurement of ANC. If ANC is >1500 unit, then MMF may be restarted at the "Step 1" dose according to what the participant's previous MMF dose was. For example, if the participant's dosage of MMF was *2.0* g/day at the time of interruption of MMF, then MMF should be restarted at *1.5* g/day. If a participant experiences an infectious complication, MMF should be stopped until the episode has resolved. MMF can then be restarted at the previous dose.

Regardless of dose reduction, every attempt must be made to bring the participant's dosage of MMF as close to 1200 mg/m^2/day as possible.

Table A10-5 Protocol-Specified MMF Dose Reduction

MMF Dosage (mg/day)	Step 1 Reduction (mg)	Step 2 Reduction (mg)
2000	1500	1000
1500	1000	500

MMF = mycophenolate mofetil.

If a participant develops an increase in serum creatinine level > 30% of baseline, MMF should be withheld. The investigator should consult with the Medical Monitor before restarting MMF.

REFERENCE

CellCept® (mycophenolate mofetil) U.S. Package Insert, Genentech.

Appendix 11 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

Appendix 12
International Clinical Practice Guidelines for the Diagnosis of Childhood-Onset FRNS or SDNS

The definitions relating to nephrotic syndrome are based on clinical characteristics and recurrence of nephrotic range proteinuria. In children relapse is commonly assessed via urine dipstick and is thus defined as dipstick urinalysis ≥ 3 ± for 3 consecutive days.

KDIGO 2021 Diagnosis Definitions (KDIGO 2021):

- *Frequently relapsing nephrotic syndrome (FRNS): ≥ 2 relapses per 6 months within 6 months of disease onset or ≥ 4 relapses per 12 months in any subsequent 12 month period*
- *Steroid-dependent nephrotic syndrome (SDNS): two consecutive relapses during therapy with prednisone or prednisolone (either at full dose or during tapering) or within 15 days of prednisone of prednisolone discontinuation*

IPNA 2023 Diagnosis Definitions (Trautmann et al. 2023):

- *Frequently relapsing nephrotic syndrome (FRNS): ≥ 2 relapses per 6 months following remission of the initial episode or ≥ 3 relapses in any 12 months*
- *Steroid-dependent nephrotic syndrome (SDNS): two consecutive relapses during recommended prednisone or prednisolone therapy for first presentation or relapse, or within 14 days of its discontinuation*

REFERENCES

[KDIGO] Kidney Disease: Improving Global Outcomes Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int 2021;100:S1–276.

Trautmann, A., Boyer, O., Hodson, E. et al. IPNA clinical practice recommendations for the diagnosis and management of children with steroid-sensitive nephrotic syndrome. Pediatr Nephrol 2023;38:877–919.

Appendix 13
Investigational Medicinal Product and Non-Investigational Medicinal Product Designations (for Use in European Economic Area)

Table A13-1 Investigational, Authorized Auxiliary, and Unauthorized Auxiliary Medicinal Product Designations for European Economic Area

Product Name	*IMP/AxMP Designation*	*Marketing Authorization Status in EEA*	*Used within Marketing Authorization*
Gazyva® (RO5072759)	*IMP (test product)* [a]	*Authorized*	*No* [b]
Cellcept (mycophenolate mofetil)	*IMP (comparator)*	*Authorized*	*No* [c]
Prednisone	*AxMP (background treatment/standard of care)*	*Authorized*	*Yes*
[redacted]	*AxMP (other)* [d]	*Authorized*	*Yes*
	AxMP (other) [d]	*Authorized*	*Yes*
	AxMP (other) [d]	*Authorized*	*Yes*

AxMP = auxiliary medicinal product; EEA = European Economic Area; IMP = investigational medicinal product; MMF= mycophenolate mofetil.

[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 and not for childhood-onset idiopathy nephrotic syndrome .*

[c] *Mycophenolate mofetil (MMF) not approved in the studied indication but recommended as per clinical treatment guidelines ([KDIGO] 2021). MMF will be administered with prednisone considered standard of care*

[d] [redacted]

Appendix 14
Abbreviations

Abbreviation or Term	Definition
ADA	anti-drug antibody
AUC	area under the curve
ADA	anti-drug antibody
BID	twice a day
[redacted]	
BSA	body surface area
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
ClinRO	clinician-reported outcome
CLL	chronic lymphocytic leukemia
C_{max}	maximum serum concentration
CMH	Cochran-Mantel-Haenszel
CNI	calcineurin inhibitor
CCOD	common close out date
CureGN	Cure Glomerulonephropathy
COVID-19	coronavirus disease 2019
IMP	investigational medicinal product
INS	idiopathic nephrotic syndrome
IRB	Institutional Review Board
IRR	Infusion-related reaction
IRT	*Interactive Response Technology*
IxRS	interactive voice or web-based response system
EC	Ethics Committee
eCRF	electronic Case Report Form
eGFR	estimated glomerular filtration rate
FL	follicular lymphoma
FRNS	frequently relapsing nephrotic syndrome
FSGS	focal segmental glomerulosclerosis
JAK	Janus-associated kinase
KDIGO	Kidney Disease Improving Global Outcomes Guidelines

Abbreviation or Term	Definition
LLN	lower limit of normal
LPLV	last participant last visit
MCD	minimal change disease
MCID	*minimal clinically important difference*
MMF	mycophenolate mofetil
MN	mobile nursing
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSAID	non-steroidal anti-inflammatory drug
NS	nephrotic syndrome
PD	pharmacodynamic
PedsQL	Pediatric Quality of Life Inventory
PK	pharmacokinetic
PO	orally
PRO	Participant-reported outcome
PT-INR	*Prothrombin Time and International Normalized Ratio*
PTT	*Prothrombin Time Test*
RFS	relapse free-survival
[redacted]	
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SDNS	steroid dependent nephrotic syndrome
SFU	safety follow-up
SGA	Subject Global Assessment of Disease Activity
[redacted]	
SLE	systemic lupus erythematosus
TB	tuberculosis
TYK2	tyrosine kinase 2
UA	urinalysis
ULN	upper limit of normal
UPCR	urine protein creatinine ratio
VAS	visual analogue scale

Appendix 15
Protocol Amendment History

A rationale for the current amendment precedes the Table of Contents.

PROTOCOL AMENDMENT, VERSION 2: (24 AUGUST 2022)

Protocol WA43380 amended primarily [redacted]. Substantive changes to the protocol, along with a rationale for each change, are summarized below.

- Sample size was increased from 72 to approximately 80 participants to increase statistical power to achieve primary and secondary endpoints and to account for inclusion of participants from China and Japan (Sections 1.1, 1.2, 4.1, 5, and 9.2).
- Vital signs taken during monitoring of participants after initial and subsequent obinutuzumab infusions will now be taken every 30 minutes throughout the designated period after the infusion while patients are being monitored until the IV line is removed rather than during the first 30 minutes after the infusion is complete (Section 1.3, Tables 1 and 3).
- The Week 2 visit has been clarified to allow both participants receiving obinutuzumab and participants who are newly initiating MMF at study onset to have labs (chemistries and CBC) drawn for MMF monitoring. (Section 1.3, Table 1, Appendix 10).
- Secondary endpoints and exploratory objectives related to patient-reported outcomes were clarified; all age-specific PROs were added; and all PROs have been consolidated (Section 3, Appendix 5).
- Hemoglobin and platelet count exclusionary cutoffs have been adjusted in the exclusion criteria to better reflect age-specific lower limit of laboratory normal or panic alerts in a childhood population (Section 4.2).
- Inclusion criteria have been updated to align with the MMF label (Section 5.1).
- For further clarity, evidence of any significant or uncontrolled cardiac disease has been specifically added to the exclusion criteria (Section 5.2).
- For accuracy and clarity, belimumab and daratumamab were moved from "any biology therapy" to "any biologic B cell-targeted therapy" in the exclusion criteria (Section 5.2).
- For further clarity, additional text for investigators was added related to rescue medication use at the time of relapse (Section 6.1.4).
- Neutropenia and thrombocytopenia thresholds for permanent treatment discontinuation have been updated to rectify a previous administrative error (Section 7.1).
- Updates were made to the statistical analysis related to primary/secondary endpoints and intercurrent event definitions (Section 9).

- An Independent Data Monitoring Committee (iDMC) will be formed to monitor and evaluate participant safety throughout the study (Appendix 1).
- The Sponsor record retention policy has been clarified (Appendix A1–7).
- Language has been added to reflect that in addition to the NCI CTCAE, intensity of adverse events will be assessed as mild, moderate, severe or life-threatening in order to allow for appropriate grading of adverse events in this patient population (Appendix A2–3.2).
- [redacted]
- In Appendix 10, guidelines for mycophenolate mofetil (MMF) dosing were modified to clarify the following in order to minimize toxicity and ensure appropriate monitoring:
  - Participants who enter the study and are naïve to MMF will be initiated below the target dose to allow for uptitration to the target dose.
  - Dose escalation of MMF will occur by uptitration to the target dose within four weeks according to local MMF treatment guidelines for the age and weight of the participant recognizing that BSA may be as low as 0.5 m^2 for younger pediatric patients.
  - The maximum dose of MMF for a relapse event will be 2.5 grams/day or 1200 mg/m^2/day, whichever is lower. The maximum dosage of 2 grams/day will be maintained for usage of MMF outside of a relapse event.
- Recommendations regarding specific medications to treat non-infectious diarrhea have been removed given that the safety and effectiveness of medications proposed are not established in pediatric patients. Instead, the recommendation was modified to allow for investigators to treat non-infectious diarrhea at their discretion as per local clinical practice (Appendix 10).
- MMF capsules instead of tablets will be used in China and this clarification has been added throughout the protocol.
- The Medical Monitor has been updated throughout the protocol.

Signature Page for Protocol - WA43380 - GAZYVA - v3 - Global/Core - Published
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Approval Task	[redacted] Company Signatory 29-May-2023 10:38:44 GMT+0000