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STATISTICAL ANALYSIS PLAN

STUDY 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**

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STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

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STATISTICAL ANALYSIS PLAN VERSION HISTORY

This Statistical Analysis Plan (SAP) was developed based on Roche SAP model document updated on 01 May 2024.

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
4	see electronic date stamp on the last page of this document	Version 3.0, 29 May 2023
3	1 July 2024	Version 3.0, 29 May 2023
2	8 November 2023	Version 3.0, 29 May 2023
1	8 November 2022	Version 2.0, 24 August 2022

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

Key changes to the Statistical Analysis Plan (SAP), along with the rationale for each change, are summarized below.

Section	Description of Change	Rationale for Change
1.1, 4.2.2, 4.3	Change of missing data handling strategy for primary endpoint and secondary binary endpoints	[redacted] on SAP V3. Due to the small number of patients on study and the small amount of missing urine protein creatinine ratio (UPCR) data anticipated given UPCR is an objective measure, there were concerns that the proposed multiple imputation approach would encounter convergence issues. As an alternative, simpler approach, a non-responder imputation will be implemented, alongside a tipping point analysis.
1.1, 4.2, 4.3	Change of handling method for the intercurrent event of treatment discontinuation	[redacted] on SAP V3. Treatment discontinuation for any reason will now be handled using treatment policy, as opposed to composite strategy. Further intercurrent events occurring after the treatment discontinuation will be handled appropriately.
4.2.4	Removal of the following supplementary analysis of the primary endpoint: Effect of Obinutuzumab vs MMF on Primary Endpoint Regardless of Treatment Discontinuation Due to Lack of Efficacy	Previously, all treatment discontinuations other than those due to AE were handled using a composite strategy i.e., caused the patient to be a non-responder. This supplementary analysis was to be implemented to explore the impact of treatment discontinuations on the primary endpoint by handling these using treatment policy. Now that all treatment discontinuations will be handled using treatment policy, this supplementary analysis no longer has merit.
4.3.1.3	Updated methodology for multiple imputation approach for patient reported outcome (PRO) endpoints.	[redacted] on SAP V3. The number of covariates within the imputation model has been reduced for the following endpoints: Mean Change in Cure Glomerulonephropathy Network (CureGN) Edema Scale from Baseline to Week 52, Mean Change in "General Fatigue" Domain of Pediatric Quality of Life Inventory (PedsQL)-Multidimensional Fatigue Scale Total Score from Baseline to Week 52 and Mean Change in "Physical Functioning"

Section	Description of Change	Rationale for Change
		Domain of PedsQL from Baseline to Week 52. Additionally, if convergence issues arise due to only using patients that did not experience an intercurrent event in the imputation model, data from all patients will be utilized instead. Example SAS code has also been provided in the appendix.
4.3.1.1, 4.3.1.2, 4.3.1.3	Updated missing data handling approach for endpoints that use UPCR as a component of the relapse definition.	[redacted] on SAP V3. If all UPCR assessments for the definition of relapse are missing, non-responder imputation will be implemented i.e. the participant will be considered to have had a relapse. A sensitivity analysis employing worst observation carried forward will be implemented i.e. for missing values, the participant's worst previous value of UPCR will be used in the relapse definition. This change will be implemented for the following endpoints: Overall Relapse Free Survival (RFS), Probability of RFS at Week 52, proportion of participants experiencing edema-associated relapse during the 52 week treatment period and number of Relapses from Baseline to Week 52.
4.5	Safety outputs will include data until the point of rescue for the patients who receive rescue therapy (excluding systemic corticosteroid rescue). Limited key safety outputs will be produced for post-rescue data.	To increase the clarity of data interpretation for safety analyses.
4.5	Limited key safety outputs will be produced including data collected after the 52 Week open-label treatment period until the CCOD.	To allow for analysis and interpretation of safety data post Week 52.
4.5.1	Update to the definition of Obinutuzumab treatment duration when calculating the duration of exposure to study treatment	Although the final protocol-mandated obinutuzumab dose is at Week 26, the definition of obinutuzumab duration of treatment exposure has been updated to reflect the duration of exposure beyond the last dose to Week 52, based on half-life, drug clearance and long lasting pharmacodynamic effects

Additional minor changes have been made throughout to improve clarity and consistency.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
ADA	anti-drug antibody
AE	adverse event
ANCOVA	analysis of covariance
BID	twice a day
BMI	body mass index
CCOD	clinical cutoff date
ClinRO	clinician-reported outcome
CMH	Cochran-Mantel-Haenszel
CSR	Clinical Study Report
CureGN	Cure Glomerulonephropathy Network
eCRF	electronic Case Report Form
eGFR	estimated glomerular filtration rate
FCS	fully conditional specification
FRNS	frequently relapsing nephrotic syndrome
HR	hazard ratio
HSFC	highly sensitive flow cytometry
iDMC	Independent Data Monitoring Committee
Ig	immunoglobulin
INS	idiopathic nephrotic syndrome
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MMF	mycophenolate mofetil
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PD	pharmacodynamic
PedsQL	Pediatric Quality of Life Inventory
PK	pharmacokinetic
PRO	patient reported outcome
PT	preferred term
RFS	relapse-free survival
SAE	serious adverse event
SAP	Statistical Analysis Plan
SDNS	steroid dependent nephrotic syndrome
SFU	safety follow-up

SOC	system organ class
TBNK	T-, B-, natural killer–cell
UA	urinalysis
ULOQ	upper limit of quantitation
UPCR	urine protein creatinine ratio
VAS	Visual Analogue Scale

1. INTRODUCTION

The analyses described in this Statistical Analysis Plan (SAP) will supersede those specified in the current published version of Protocol WA43380 for the purposes of a regulatory filing.

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.

The primary efficacy endpoint is the proportion of participants with sustained complete remission at 1 year, defined as first morning void urine protein creatinine ratio (UPCR) ≤0.2 g/g at Week 52 without occurrence of relapse or any other intercurrent event (except treatment discontinuation for any reason). Key secondary endpoints include the effect of obinutuzumab on overall relapse-free survival (RFS), probability of RFS at Week 52, cumulative corticosteroid dose, number of relapses from baseline to Week 52, proportion of participants experiencing edema-associated relapses during the 52-week treatment period, mean change in Cure Glomerulonephropathy Network (CureGN) Edema scale from baseline to Week 52, mean change in "General Fatigue" domain of Pediatric Quality of Life Inventory (PedsQL)-Multidimensional Fatigue scale total score from baseline to Week 52, mean change in "Physical Functioning" domain of PedsQL from baseline to Week 52, and proportion of patients in sustained complete remission at Week 76.

Changes to the protocol-planned analyses are described in Section 4.8.

1.1 TRIAL OBJECTIVES, ENDPOINTS, AND ESTIMANDS

This study will evaluate the efficacy, safety, PK and PD of obinutuzumab compared with MMF in participants aged ≥2–25 years old with childhood-onset FRNS or SDNS. Specific objectives and corresponding endpoints for the study are outlined in Table 1. In this protocol, "study treatment" refers to the treatments assigned to participants as part of this study (i.e., obinutuzumab or MMF).

Table 1 Primary and Key Secondary Objectives and Corresponding Estimands

Primary Objective	Estimand Definition
To evaluate the efficacy of obinutuzumab compared with MMF	**Proportion of Participants with Sustained Complete Remission at 1 Year** • **Population:** Patients with FRNS or SDNS • **Treatments:** o Obinutuzumab arm (Group A): Obinutuzumab 1000 mg IV (or 20 mg/kg for participants < 45 kg) on Days 1, 15, 168 (Week 24), and Day 182 (Week 26) o 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 (except treatment discontinuation for any reason) • **Intercurrent Events:** Intercurrent event defined as any of the following occurring after Week 8: o 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 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 o Any systemic corticosteroids usage for >14 days in a 30 day period Intercurrent events defined as events occurring after randomization: o Initiation of any rescue therapy for INS, other than systemic corticosteroids, as determined by the investigator's best medical judgement o Treatment discontinuation for any reason o Death

	• **Strategy for intercurrent events** o All intercurrent events (except treatment discontinuation for any reason) have been incorporated in the definition of the primary endpoints using the composite variable strategy, i.e., any occurrence of intercurrent events before the primary assessment will cause the patient to be counted as a non-responder. o The intercurrent event of treatment discontinuation for any reason will be dealt with using the treatment policy strategy (i.e., the actual observations after the occurrence of the intercurrent event will be used for the analysis and the patient will not be counted as a non-responder). • **Population-level summary measure:** Difference in the proportion of participants in sustained complete remission at Week 52

Key Secondary Objectives	**Estimand Definition**
To evaluate the efficacy of obinutuzumab compared with MMF	**<u>Overall Relapse-Free Survival (RFS)</u>** • **Population:** See primary endpoint. • **Treatments:** See primary endpoint. • **Variable:** Overall RFS (including all available data at the CCOD) defined as the time from randomization to first relapse or death. Relapse is defined by any of the following events: o First-morning void UPCR ≥2 g/g **or** o 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** o 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 • **Intercurrent events and handling strategy:** The following intercurrent events are treated as part of the definition of this time-to-event endpoint described above: o Death The following intercurrent events will be censored: o Patients who withdraw their consent will be censored at the time of withdrawal o Patients who are lost to follow-up will be censored at the last assessment during scheduled or unscheduled visits

	The following intercurrent events will be dealt with using the treatment policy strategy (i.e., the actual observations after the occurrence of the intercurrent event will be used for the analysis): ○ Treatment discontinuation for any reason ○ 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 • **Population-level summary measure:** Hazard ratio and log-rank test **Probability of Relapse-Free Survival (RFS) at Week 52** • **Population:** See primary endpoint. • **Treatments:** See primary endpoint. • **Variable:** Probability of RFS at Week 52 is defined as the proportion of participants remaining free of relapse or death at Week 52. Relapse is defined as in the **Overall Relapse Free Survival (RFS)** endpoint. • **Intercurrent Events & Strategy:** See overall RFS. • **Population-level summary measure:** difference in probability of RFS at Week 52. **Proportion of Participants Experiencing Edema-Associated Relapse during the 52-Week Treatment Period** • **Population:** See primary endpoint. • **Treatments:** See primary endpoint. • **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[1] without occurrence of an intercurrent event as defined by the primary endpoint (see Section 4.2.1), prior to Week 52. • **Intercurrent Events & Strategy:** See primary endpoint.

[1] *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:** difference in proportions at Week 52. **<u>Proportion of Patients with Sustained Complete Remission at Week 76</u>** • **Population:** Patients with FRNS or SDNS who were randomized into the study at least 24 weeks prior to the date of randomization for the final patient in the study. • **Treatments:** See primary endpoint. • **Variable:** 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 relapse or any other intercurrent event (except treatment discontinuation for any reason) • **Intercurrent Events:** See primary endpoint • **Strategy for intercurrent events:** o All intercurrent events (except treatment discontinuation for any reason) have been incorporated in the definition of the primary endpoints using the composite variable strategy, i.e., any occurrence of intercurrent events before the primary assessment will cause the patient to be counted as a non-responder. o The intercurrent event of treatment discontinuation for any reason will be dealt with using the treatment policy strategy (i.e., the actual observations after the occurrence of the intercurrent event will be used for the analysis and the patient will not be counted as a non-responder). o Patients who discontinue the study early, including those who do not opt to participate in the post Week 52 treatment extension period, will also be considered as non-responders for this endpoint. • **Population-level summary measure:** Difference in the proportion of participants in sustained complete remission at Week 76 **<u>Cumulative Corticosteroid Dose from Baseline to Week 52</u>** • **Population:** See primary endpoint. • **Treatments:** See primary endpoint. • **Variable:** Cumulative corticosteroid dose defined as the total dose received (mg/kg) of prednisone or equivalent 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. Topical, intraarticular, or inhaled corticosteroids and IV methylprednisolone given as a pre-medication will not be included in this analysis.
	• **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 for any reason
	  ○ Death
	• **Strategy for Intercurrent Events:**
	  ○ While-on-Treatment Strategy will be used to deal with death (i.e., the values of the variables of interest up to the time of the intercurrent event will be used).
	  ○ All other intercurrent events (except death) will be dealt with using the treatment policy strategy (i.e., the corticosteroid dose accumulated from baseline to Week 52 will be used in the analysis regardless of the occurrence of an intercurrent event).
	• **Population-level summary measure:** difference in medians
	
	Number of Relapses from Baseline to Week 52
	• **Population:** See primary endpoint.
	• **Treatments:** See primary endpoint.
	• **Variable:** 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. Relapse is defined in the primary endpoint (see Section 4.2.1).
	• **Intercurrent Events:**
	  ○ 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 for any reason

	○ Death • **Strategy for Intercurrent Events:** ○ While-on-Treatment Strategy will be used to deal with the intercurrent events of death and initiation of any rescue therapy for INS other than systemic corticosteroids (i.e., the values of the variables of interests up to the time of the intercurrent event will be used). ○ All other intercurrent events (except death and initiation of any rescue therapy for INS other than systemic corticosteroids) will be dealt with using the treatment policy strategy (i.e., the number of relapses accumulated from baseline to Week 52 will be used in the analysis regardless of the occurrence of an intercurrent event). • **Population-level summary:** Adjusted rate ratio
To evaluate edema over time	**Mean Change in CureGN Edema Scale from Baseline to Week 52** • **Population:** See primary endpoint. • **Treatments:** See primary endpoint. • **Variable:** Mean Change in CureGN Edema Scale is defined as the change in total edema severity (see Section 4.6.6 for derivation of this scale) from baseline to Week 52. • **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 for any reason ○ Death • **Strategy for Intercurrent Events:** ○ Hypothetical Strategy will be used to deal with death (i.e., the values of the variables of interests will be imputed by the last observation carried forward method). ○ While-on-Treatment Strategy will be used to deal with the initiation of any rescue therapy for INS, other than systemic corticosteroids, as determined by the investigator's best medical judgement. This strategy will use the values of the variable of interest up to the time of

	the first occurrence of the above intercurrent event for the analysis. o 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, i.e., the values of the variables of interest measured after the occurrence of this intercurrent event will be used. • **Population-level summary:** difference in adjusted means at a specified timepoint of visit.
To evaluate changes in fatigue of participants treated with obinutuzumab compared with MMF	**Mean Change in "General Fatigue" Domain Score of PedsQL-Multidimensional Fatigue Scale from Baseline to Week 52** • **Population:** See primary endpoint. • **Treatments:** See primary endpoint. • **Variable:** Mean Change in "General Fatigue" (see Section 4.6.6 for derivation of this scale) domain score of PedsQL-Multidimensional Fatigue scale is defined as the mean change in the total score on the "General Fatigue" domain of the PedsQL-Multidimensional Fatigue scale from baseline to Week 52. • **Intercurrent Events:** See mean change in CureGN Edema scale from baseline to Week 52. • **Strategy for Intercurrent Events:** See mean change in CureGN Edema scale from baseline to Week 52. • **Population-level summary:** difference in adjusted means at a specified timepoint of visit.
To evaluate changes in the quality of life of participants treated with obinutuzumab compared with MMF	**Mean Change in "Physical Functioning" Domain of PedsQL from Baseline to Week 52** • **Population:** See primary endpoint. • **Treatments:** See primary endpoint. • **Variable:** Mean change in "Physical Functioning" (see Section 4.6.6 for derivation of this scale) domain of PedsQL is defined as the mean change in the Physical Functioning domain score on the PedsQL from baseline to Week 52. • **Intercurrent Events:** See mean change in CureGN Edema scale from baseline to Week 52. • **Strategy for Intercurrent Events:** See mean change in CureGN Edema scale from baseline to Week 52. • **Population-level summary:** difference in adjusted means at a specified timepoint of visit.

AE = adverse event; BID = twice a day; CCOD = clinical cutoff date; CureGN = Cure Glomerulonephropathy Network; eCRF = electronic Case Report Form; FRNS = frequently relapsing nephrotic syndrome; INS = idiopathic nephrotic syndrome; IV = intravenous; MMF = mycophenolate mofetil; PedsQL = Pediatric Quality of Life Inventory; RFS = relapse-free survival; SDNS = steroid dependent nephrotic syndrome; UA = urinalysis; UPCR = urinary protein-to-creatinine ratio.

Table 2 Supportive Secondary and Exploratory Objectives

Secondary Objectives	Corresponding Endpoints
• To evaluate the safety of obinutuzumab compared with MMF	• Incidence, nature and severity of AEs, 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 peripheral CD19+ B cell depletion (HSFC) at specified timepoints • Total peripheral B cell and B cell subset (e.g., memory B cells) counts and change from baseline at specified timepoints
• To evaluate the efficacy of obinutuzumab compared with MMF	• Change of the UPCR from baseline to Week 52 • Change of eGFR from baseline to Week 52 • Proportion of participants achieving sustained peripheral B cell depletion at Weeks 24, 52, and 76 • Proportion of participants who achieve RFS at Week 24 with successful protocol-defined steroid taper
Exploratory Objectives	**Corresponding Endpoints**
	• [redacted]
• [redacted]	• [redacted]



AE = adverse event; HSFC = high sensitivity flow cytometry; MMF = mycophenolate mofetil; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PD = pharmacodynamic; RFS = relapse-free survival; UPCR = urinary protein-to-creatinine ratio;

1.2 STUDY 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.

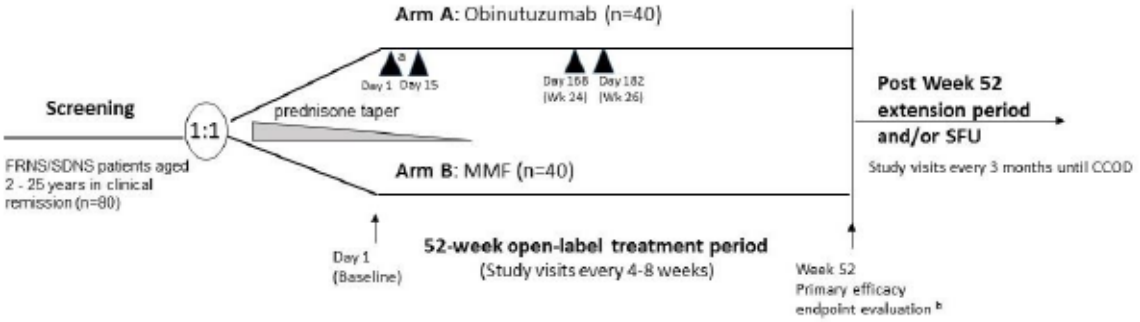
Participants aged ≥2–25 years old at the time of signing informed consent must be in complete remission defined by the absence of edema, a UPCR ≤0.2 g/g at the screening visit and have 3 consecutive daily (home-monitoring) urine dipstick readings of trace or negative for protein within the week prior 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 of Protocol), a 52-week initial open-label treatment period (see Section 4.1.2 of Protocol), a post-Week 52 extension period (see Section 4.1.3 of Protocol), 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 of Protocol). A study schema is provided below (see Figure 1). A schedule of activities and sample collection schedule is provided in Table 1, Table 2, and Table 3 of the Protocol.

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 of the Protocol) until the clinical cutoff date (CCOD) for the primary analysis. Randomization will be stratified by the participant's disease type (FRNS vs. SDNS) and the use of immunosuppressive treatment, other than corticosteroids for idiopathic nephrotic syndrome (INS) prior to study entry (MMF/other immunosuppressive agent vs. no MMF/other immunosuppressive agent).

The primary endpoint analysis will occur when the last participant reaches the Week 52 study visit of the open-label treatment period. If the last patient withdraws from the study prior to Week 52, the primary endpoint analysis will occur when the previously randomized patient reaches the Week 52 study visit of the open-label treatment period. Data for the post-Week 52 open-label period and SFU period will be reported separately in subsequent reporting events. Note that, at the time of the primary analysis, the endpoints of "Overall Relapse Free Survival" and "Proportion of Patients in Sustained Complete Remission at Week 76" will present data from the post-Week 52 open-label treatment period.

Figure 1 Study Schema



▲ **Arm A**: Obinutuzumab infusion: 1000 mg or 20 mg/kg if < 45kg on Day 1, Day 15, Day 168 (Wk 24), and Day 182 (Wk 26)
Arm B: MMF PO dose 600 mg/m^2 BID (target 1200 mg/m^2/day in divided daily doses) until Wk 52.
After Wk 52, MMF may be discontinued or tapered over the subsequent 3 months.

All patients may receive oral prednisone or equivalent (40 mg/m^2 or 1.5 mg/kg; maximum 50 mg day) with goal to taper to target dose of 0 mg by Wk 8.

BID = twice a day; CCOD = clinical cutoff date; 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 1) will be measured at Week 52.

1.2.1 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 interactive voice/web-based response system (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. Randomization will be stratified according to the following criteria:

- Disease type
  - FRNS
  - SDNS
- Use of immunosuppressive treatment, other than corticosteroids for INS, prior to study entry
  - MMF/other immunosuppressive agent
  - No use of MMF/other immunosuppressive agent

1.2.2 Independent Review Facility

No Independent Review Facility is planned for this study.

1.2.3 Data Monitoring

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. After each safety review, if a relevant safety signal is observed, the iDMC may consider recommending continuing the study without modifications, continuing the study with recommended modifications, stopping the study, or putting enrollment on hold pending further iDMC recommendations. A detailed plan will be included in the finalized iDMC charter.

2. STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION

2.1 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 relapse or any other intercurrent event (except treatment discontinuation for any reason).

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 complete remission at Week 52, without occurrence of relapse or any other intercurrent event (except treatment discontinuation for any reason) after the initial prednisone taper, for obinutuzumab and MMF respectively. The definition of intercurrent events can be found in Section 4.2.1.

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 the multiplicity for the overall type I error, a fixed sequence testing procedure will be used (Westfall and Krishen 2001). The primary and key secondary endpoints will be tested in the order shown below at a two-sided 5% significance level, proceeding sequentially starting from the primary endpoint and testing each key secondary endpoint after achieving statistical significance on the previous endpoint.

The sequence for endpoint testing will be the primary endpoint followed by the key secondary endpoints in the following order:

1. Overall RFS (including all available data at the CCOD) defined as the time from randomization to first relapse or death
2. Cumulative corticosteroid dose from baseline to Week 52
3. Number of relapses from baseline to Week 52
4. Proportion of patients 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 (except for treatment discontinuation for any reason)
5. Probability of RFS at Week 52
6. Proportion of participants experiencing edema-associated relapse during the 52-week treatment period
7. Mean change in CureGN Edema scale from baseline to Week 52
8. Mean change in "General Fatigue" domain of PedsQL-Multidimensional Fatigue scale total score from baseline to Week 52
9. Mean change in "Physical Functioning" domain of PedsQL from baseline to Week 52

2.2 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.

Participants in both treatment groups may receive a tapering course of oral corticosteroids in addition to their randomized treatment (see Section 6.1.3 of Protocol). 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

[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.

Week 52 without occurrence of relapse or any other intercurrent event (except treatment discontinuation for any reason) (see Table 1). Assuming 72.5% of participants in obinutuzumab group and 40% participants in 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 approximately 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.

In order to preserve the Type I error and adjust for multiplicity due to multiple endpoints, a fixed sequence testing procedure will be used (see Section 2.1).

2.2.1 Sample Size for China Subpopulation

This study will enroll approximately 10 participants across all sites in China. After completion of the global enrollment phase, additional participants may be enrolled in a potential extended China enrollment phase to ensure a total of approximately 10 participants in the China subpopulation. The global population includes all participants enrolled during the global enrollment phase (including participants enrolled during that phase), and the China subpopulation includes all participants enrolled in China (during both the global enrollment phase and the extended China enrollment phase).

3. ANALYSIS SETS

The following analysis sets are defined:

Table 3 Participant Analysis Sets

Participant Analysis Set	Description
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.

Participant Analysis Set	Description
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.

4. STATISTICAL ANALYSES

4.1 GENERAL CONSIDERATIONS

Statistical hypothesis testing will be conducted on the primary endpoint and key 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 5% significance level. Summary statistics, including mean, median, standard deviation, and range, will be reported for continuous endpoints.

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 for any reason, and death. The definition of intercurrent events can be found in Table 1. The methods to handle the intercurrent events are provided with the description of the estimands for the primary and key secondary endpoints, respectively.

The following general considerations will be accounted for in the analysis unless otherwise specified:

- The stratification factors of disease type (FRNS vs. SDNS) and use of immunosuppressive treatment, other than corticosteroids for INS prior to study entry (MMF/other immunosuppressive agent vs. no MMF/other immunosuppressive agent).
- Data collected at scheduled and unscheduled visits will be mapped to visits that appear in the schedule of activities (see Section 1.3 of Protocol). Visit windows will be continuous from the midpoint between two consecutive study visits, and will be dependent on the schedule of activities for each test independently.
- If there are multiple values in the same window, values closest to the scheduled study day will be used in the analysis.
- For each participant, the day of first study drug administration will be designated Study Day 1. Each assessment will be assigned a study day calculated as:

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

- Baseline is defined as the last non-missing value prior to the receipt of any dose of study treatment. Typically, baseline will be the pre-dose Day 1 assessment, but may include screening results if the pre-dose Day 1 result is not available or missing.
- In general, laboratory data that are continuous in nature but are less than the lower limit of quantification (LLOQ); i.e. reported as "< LLOQ", will be set to the LLOQ/2. Similarly, continuous laboratory data that are higher than the upper limit of quantification (ULOQ); i.e., reported as "> ULOQ", will be set to the ULOQ. .
- For the intercurrent event of any systemic corticosteroid usage for >14 days in a 30 day period, the time at which a patient would be considered to have experienced this intercurrent event would be Day 15 of steroid usage within the 30 day period in which systemic corticosteroids were used for >14 days.

Missing Data on Steroid Use

Missing data on steroid use will be minimized via several measures implemented within the electronic Case Report Form (eCRF) and data review. The methodology for addressing any remaining intermittent missing data on steroid use is outlined below.

Within a course of steroid therapy, if there are any dates for which there is no entry of steroid dose given and the investigator has not indicated that the course of steroid was completed (using a checkbox on the eCRF), it will be assumed that the patient received steroid at the last known dose until indicated otherwise. Some examples are provided below to illustrate this procedure.

Example Patient 1

Study Day Start	Study Day End	Dose (mg)	Steroid Tapered?
104	107	40	No
109	116	20	No
118	123	10	Yes

In this example, on Study Days 108 and 117, there is missing data as there is no entry for steroid dose and the current course was not completed (steroid tapered=No). Under the missing data procedure, it would therefore be assumed that this patient received 40 mg of steroid on Study Day 108 and 20 mg on Study Day 117.

Example Patient 2

Study Day Start	Study Day End	Dose (mg)	Steroid Tapered?
110	117	40	No
118	126	20	No
127	133	10	Yes
152	157	40	No
158	163	20	Yes

In this example, there is no missing data

Example Patient 3

Study Day Start	Study Day End	Dose (mg)	Steroid Tapered?
110	117	40	No
118	126	20	No
127	133	10	No
152	157	40	No
158	163	20	Yes

In this example, there is missing data between Study Day 133 and 152 as there was no evidence that the course of steroid was tapered. It would therefore be assumed that this patient received 10 mg of steroid from Study Day 134 to 151.

4.1.1 Patient Disposition

Enrollment, treatment discontinuation, treatment discontinuation reasons, study discontinuation, and reasons for discontinuation from the study will be summarized by treatment arm.

4.2 PRIMARY ENDPOINT ANALYSIS

4.2.1 Definition of Primary Endpoint

The primary endpoint/estimand is 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 (except treatment discontinuation for any reason). Further details can be found in Section 1.1 of this SAP (see Table 1).

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

- **Population:** Patients with FRNS or SDNS
- **Treatments:** Obinutuzumab arm or MMF arm
    - Obinutuzumab arm (Group A): Obinutuzumab 1000 mg IV (or 20 mg/kg for participants <45 kg) on Days 1, 15, 168 (Week 24), and Day 182 (Week 26)
    - MMF arm (Group B): 600 mg/m^2 twice a day (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 (except treatment discontinuation for any reason)
- **Population-level summary measure:** Difference in the proportion of participants in sustained complete remission at Week 52
- **Intercurrent events occurring after Week 8:** The following events are not considered intercurrent events prior to Week 8
    - Relapse as defined by any of the following events:

- First-morning void UPCR ≥2 g/g **or**
- Dipstick urinalysis (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:** The following events are considered intercurrent events from randomization.
  - Initiation of any rescue therapy for INS, as determined by the investigator's best medical judgement, other than systemic corticosteroids
  - Treatment discontinuation for any reason
  - Death

Strategy for Intercurrent Events

[redacted]

4.2.2 Main Analytical Approach for Primary Endpoint

The difference in proportion of sustained complete remission at Week 52 between obinutuzumab and MMF arms will be reported, along with the 95% Newcombe CI. The statistical test for significance will be performed using the CMH test for the common risk difference, 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. The adjusted difference in proportions and the Newcombe CI will be calculated using Mantel-Haenszel weights. See Appendix 3 for example SAS code detailing how this analysis will be implemented.

A non-responder imputation will be implemented to handle missing data for the primary endpoint. Participants with missing UPCR at Week 52 will be considered as

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

non-responders for the primary endpoint. The non-responder imputation will be applied after all ICE handling strategies have been implemented.

4.2.3 Sensitivity Analysis

To assess the robustness of the primary estimand to missing data assumptions, the following sensitivity analyses will be evaluated.

Last observation carried forward (LOCF)/Non-Responder: Missing UPCR at Week 52 will be imputed with UPCR at Week 40. If the Week 40 UPCR is missing, then the participant will be set to non-responder. A tipping point analysis will also be conducted by varying assumptions about the missing outcomes in the obinutuzumab and MMF arms.

4.2.4 Supplementary Analysis

To further support interpretation of the primary endpoint, the proportion of patients experiencing an intercurrent event (relapse, systemic corticosteroids usage, rescue therapy, treatment discontinuation for any reason, and death) will be summarized descriptively.

4.2.4.1 Effect of Obinutuzumab vs MMF on Primary Endpoint Regardless of Adherence to Steroid Taper

A supplementary analysis will be conducted in order to characterize the effect of steroid reduction on the primary endpoint. Participants who would normally be considered non-responders if they do not complete the protocol-defined steroid taper (i.e., still receiving systemic corticosteroid after Week 8 for 14 days or more in a 30-day period), will instead be assessed at Week 52 for the primary endpoint under the treatment policy strategy.

The estimand attributes for this supplementary analysis are as follows:

- **Population:** See Section 4.2.1
- **Treatments:** See Section 4.2.1
- **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 a relapse or any other intercurrent event (except for treatment discontinuation for any reason and any systemic corticosteroid usage for >14 days in a 30 day period).
- **Population-level summary measure:** See Section 4.2.1
- **Intercurrent events occurring after Week 8:**
    - Relapse as defined by any of the following:
        - First-morning void UPCR ≥2 g/g **or**

- Dipstick urinalysis (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

- **Intercurrent events occurring after randomization:** See Section 4.2.1

Strategy for Intercurrent Events

All intercurrent events (except treatment discontinuation for any reason and any systemic corticosteroids usage for >14 days in a 30 day period) have been incorporated in the definition of the primary endpoint using the composite variable strategy, i.e., any occurrence of intercurrent events before the primary assessment will cause the patient to be counted as a non-responder. The intercurrent events of treatment discontinuation for any reason and any systemic corticosteroids usage for >14 days in a 30 day period will be dealt with using the treatment policy strategy (i.e., the actual observations after the occurrence of the intercurrent event will be used for the analysis).

Main Analytical Approach

The difference in proportion of sustained complete remission at Week 52 between obinutuzumab and MMF arms will be reported, along with the 95% Newcombe CI. No statistical hypothesis testing will be conducted for the supplementary analysis. Missing data will be imputed as per Section 4.2.2.

4.2.4.2 Effect of Obinutuzumab vs MMF on Primary Endpoint Regardless of Completion of Protocol Defined Steroid Taper or Systemic Corticosteroid Usage

The estimand attributes for this supplementary analysis are as follows:

- **Population:** See Section 4.2.1
- **Treatments:** See Section 4.2.1
- **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 a relapse or death
- **Population-level summary measure:** See Section 4.2.1
- **Intercurrent events occurring after Week 8:** See Section 4.2.1
- **Intercurrent events occurring after randomization:** See Section 4.2.1

Strategy for Intercurrent Events

The intercurrent events of relapse and death have been incorporated in the definition of the primary endpoint using the composite variable strategy, i.e., any occurrence of intercurrent events before the primary assessment will cause the patient to be counted as a non-responder. All other intercurrent events (treatment discontinuation for any

reason, any systemic corticosteroids usage for >14 days in a 30-day period, initiation of any rescue therapy for INS) will be dealt with using the treatment policy strategy, i.e., the actual observations after the occurrence of the intercurrent event will be used for the analysis.

Main Analytical Approach

The difference in proportion of sustained complete remission at Week 52 between obinutuzumab and MMF arms will be reported, along with the 95% Newcombe CI. No statistical hypothesis testing will be conducted for the supplementary analysis. Missing data will be imputed as per Section 4.2.2.

4.2.4.3 Subgroup Analyses for Primary Endpoint

The generalizability of sustained complete remission results when comparing obinutuzumab to MMF will be investigated by estimating the treatment effect in the following subgroups via forest plots:

- Disease type (FRNS vs. SDNS)
- Previous use of immunosuppressive treatment other than corticosteroids for INS (MMF/other immunosuppressive agent vs. no MMF/other immunosuppressive agent)
- Age (<12 years vs. ≥12 years)
- Sex
- Race
- RegionWeight (<45kg vs. ≥45kg)

4.3 SECONDARY ENDPOINT ANALYSES

4.3.1 Key/Confirmatory Secondary Endpoints

Unless otherwise specified, the following attributes are the same across all key secondary endpoints (time-to-event, binary and continuous):

- **Population:** Patients with FRNS or SDNS
- **Treatments:**
  - Obinutuzumab arm (Group A): Obinutuzumab 1000 mg IV (or 20 mg/kg for participants <45 kg) 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

The other estimand attributes of intercurrent events, summary measure and analytical approach are defined differently for time-to-event, binary and continuous key secondary endpoints, and are described in Section 4.3.1.1, Section 4.3.1.2 and Section 4.3.1.3 respectively.

4.3.1.1 Time-to-Event Key Secondary Endpoints

Unless specified otherwise, the estimand attributes for time-to-event endpoints are defined as follows:

- **Population:** See Section 4.2.1
- **Treatments:** See Section 4.2.1
- **Variable:** See definition in Section 4.3.1.1
- **Population-level summary measure:** Hazard Ratio (HR) and log-rank test
- **Intercurrent events:**

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

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

Main Analytical Approach

Data will be summarized using Kaplan-Meier curves. A stratified log-rank test will be used to compare the treatment arms adjusting for the stratification factors. Median time to event (when estimable) and their 95% CIs using the Brookmeyer and Crowley method, and a p-value from the log-rank test will be presented. The HR and its 95% CI will be estimated using a Cox regression model stratified by stratification factors. In fitting the Cox model, ties will be handled with the approximate likelihood method of Efron 1977.

Missing Data

Missing components for the definition of relapse (UPCR assessments at scheduled visits at Weeks 12, 24, 40 and 52, and UPCR assessments triggered by dipstick home

monitoring) will be imputed using the following method. If all UPCR assessments for the definition of relapse are missing, non-responder imputation will be implemented i.e., the participant will be considered to have had a relapse. A sensitivity analysis employing worst observation carried forward will be implemented i.e., for missing values, the participant's worst previous value of UPCR will be used in the relapse definition.

Data Censoring

Patients who withdraw from the study will be censored at the time of study withdrawal. Patients who do not experience an event will be censored at the time of primary analysis.

Overall Relapse-Free Survival (RFS)

- **Variable:** Overall RFS (including all available data at the CCOD) defined as the time from randomization to first relapse or death. Relapse is defined by any of the following events:
  - First-morning void UPCR ≥ 2 g/g **or**
  - Dipstick urinalysis (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

Probability of Relapse-Free Survival (RFS) at Week 52

- **Variable:** Probability of RFS at Week 52 is defined as the proportion of participants remaining free of relapse or death at Week 52. The estimand attributes of intercurrent events and censoring will be defined the same as Section 4.3.1.1.
- **Population-level summary measure:** difference in probability of RFS at Week 52.
- **Main Analytical Approach:** The RFS rate at Week 52 will be estimated using Kaplan-Meier methodology, along with 95% CIs calculated using the standard error derived from Greenwood's formula. The difference in RFS rates between obinutuzumab and MMF arms will be estimated by use of the normal approximation method. The statistical test for significance will be performed using a z-test.

4.3.1.2 Binary Key Secondary Endpoints

Unless specified otherwise, the estimand attributes for binary endpoints are defined as follows:

- **Population:** See Section 4.2.1
- **Treatments:** See Section 4.2.1
- **Variable:** See respective endpoint definitions

- **Intercurrent events:** See Section 4.2.1
- **Population-level summary measure:** difference in proportion between the obinutuzumab and MMF treatment arms.

Main Analytical Approach

The proportion between obinutuzumab and MMF arms will be reported, along with the 95% Newcombe CI. The statistical test for significance will be performed using the CMH test for the common risk difference, at 5% level of significance (two-sided), with disease type and use of immunosuppressive treatment (other than corticosteroids for INS) prior to study entry as stratification factors. The adjusted difference in proportions and the Newcombe CI will be calculated using Mantel-Haenszel weights. See Appendix 3 for example SAS code detailing how this analysis will be implemented.

Proportion of Participants Experiencing Edema-Associated Relapse during the 52-Week Treatment Period

- **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], prior to Week 52
- **Strategy for Intercurrent Events:** All intercurrent events (except death) will be handled using the treatment policy strategy (i.e., the actual observations after the occurrence of the intercurrent event will be used for the analysis). The intercurrent event of death will be handled using the while-on-treatment strategy (i.e. whether the participant experienced an edema-associated relapse from randomization until the time of death)

Missing Data

The maximum analysis follow-up time to experience an edema-associated relapse is 52 weeks, or until the patient dies, whichever occurs first. If a patient dies within 52 weeks, the missing data will not be imputed. In this case, the binary value for whether or not the patient experienced an edema-associated relapse up until the time of death (Yes/No) will be used in the analysis. Missing components for the definition of relapse (UPCR assessments at scheduled visits at Weeks 12, 24, 40 and 52, and UPCR assessments triggered by dipstick home monitoring) will be imputed using the following method. If all UPCR assessments for the definition of relapse are missing, non-responder imputation will be implemented i.e. the participant will be considered to have had a relapse. A sensitivity analysis employing worst observation carried forward will be implemented i.e. for missing values, the participant's worst previous value of UPCR will be used in the relapse definition.

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[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.*

Proportion of Participants in Sustained Complete Remission at Week 76

- **Population:** Patients with FRNS or SDNS who were randomized into the study at least 24 weeks prior to the date of randomization for the final patient in the study.
- **Variable:** 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 relapse or any other intercurrent event (except treatment discontinuation for any reason)
- **Population-level summary measure:** Difference in the proportion of participants in sustained complete remission at Week 76.
- **Strategy for Intercurrent Events:** [redacted]

Justification of Estimand Population

- Upon randomization of the final patient into the study, there will be a predefined CCOD: date of randomization + 52 Weeks. Therefore all patients randomized into the study at least 24 weeks prior to the data of randomization of the final patient will have the potential to attend their scheduled Week 76 visit before the CCOD.
- This group of patients will include those who attended the Week 76 visit and therefore have data for this endpoint, those who didn't complete the scheduled Week 76 visit at or prior to the CCOD, as well as those who did not enter the post Week 52 treatment extension period but would have had a scheduled Week 76 visit prior to the CCOD.

Missing Data

A non-responder imputation will be implemented to handle missing data for the proportion of participants with sustained complete remission at Week 76. Participants with missing UPCR at Week 76 will be considered as non-responders for this endpoint.

4.3.1.3 Continuous & Count Key Secondary Endpoints

Unless specified otherwise, the estimand attributes for continuous and count endpoints are defined as follows:

- **Population:** See Section 4.2.1
- **Treatments:** See Section 4.2.1

- **Variable:** See definition in Section 4.3.1.3
- **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 for any reason
  - Death
- **Strategy for Intercurrent Events:**
  - See respective endpoint definition
- **Population-level summary measure:** See respective endpoint definition

Main Analytical Approach

The difference in adjusted means between obinutuzumab and MMF arms will be reported along with the corresponding 95% CI. The statistical test for significance will be performed using an analysis of covariance (ANCOVA) while adjusting for baseline score, and stratification factors.

Missing Data

See respective endpoint definition.

Subgroup Analyses

Endpoints associated with the PedsQL instrument (Mean Change in "General Fatigue" PedsQL, Mean Change in "Physical Functioning" PedsQL) will be evaluated across the following subgroups:

- Age 2-11 years
- Age 12-25 years

The analysis will be presented by the difference in adjusted means at Week 52 with 95% confidence intervals and p-values.

Cumulative Corticosteroid Dose from Baseline to Week 52

- **Variable:** Cumulative corticosteroid dose defined as the total dose received (mg/kg) of prednisone or equivalent 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. Topical, intraarticular, or inhaled corticosteroids and IV methylprednisolone given as a pre-medication will not be included in this analysis.
- **Strategy for Intercurrent Events:**
  - All intercurrent events (except death) will be dealt with using the treatment policy strategy for analyzing the endpoint of the cumulative corticosteroid

dose (i.e., the corticosteroid dose accumulated from baseline to Week 52 will be used in the analysis regardless of the occurrence of an intercurrent event).

  - While-on-Treatment Strategy will be used to deal with death (i.e., the corticosteroid dose accumulated up to the time of death).

- **Population Summary Measure:** difference in medians

Main Analytical Approach

The statistical test for significance will be performed on the cumulative corticosteroid dose using a Wilcoxon Mann-Whitney test, assuming that the data will be non-normally distributed. If it is found that the data follows a normal distribution using a Shapiro-Wilk test, a t-test will be used to compare the difference in the two treatment groups.

Missing Data

The maximum analysis follow-up time to accumulate corticosteroid dose is 52 weeks, or until the patient withdraws or dies, whichever occurs first. If a patient withdraws or dies within 52 weeks, the missing data will not be imputed. In this case, the cumulative corticosteroid dose up until the time of study withdrawal or death will be used in the analysis.

Number of Relapses from Baseline to Week 52

- **Variable:** 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. Relapse is defined by any of the following events:
  - First-morning void UPCR ≥ 2 g/g **or**
  - Dipstick urinalysis (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

- **Intercurrent Events:**
  - 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 for any reason
  - Death

- **Strategy for Intercurrent Events:**
  - All intercurrent events (except death and initiation of any rescue therapy for INS other than systemic corticosteroids) will be dealt with using the treatment policy strategy (i.e., the number of relapses accumulated from baseline to

Week 52 will be used in the analysis regardless of the occurrence of an intercurrent event).

- While-on-Treatment Strategy will be used to deal with the intercurrent event of death (i.e., the number of relapses accumulated from baseline up to the time of death will be used).
- While-on-Treatment Strategy will be used to deal with the intercurrent event of initiation of any rescue therapy for INS other than systemic corticosteroids (i.e., the number of relapses accumulated from baseline up to the time of the receipt of rescue therapy will be used). This strategy is considered appropriate as the use of rescue therapies, other than the assigned study drug, is expected to impact the disease progression and propensity for relapses. It is of interest to assess the patients' response to study drug prior to receiving rescue therapy.

- **Population-level summary measure:** adjusted rate ratio

Main Analytical Approach

The total number of relapses occurring during the treatment period will be evaluated by taking into account the number of relapses experienced and the participant's follow-up time (defined below). Patient level relapse and follow-up time data will then be aggregated, and the rate of relapses compared between the Obinutuzumab and MMF treatment groups. Rate of relapse will be analyzed using a negative binomial model with a log link and the log of each patient's follow-up time as an offset variable. The model will include factors for treatment, disease type, immunosuppressive treatment (other than corticosteroids for INS) prior to study entry, baseline corticosteroid dose, and baseline body weight:

$$\ln(\mu_i) = \ln(t_i) + \beta_1 + \beta_2 x_{1i} + \beta_3 x_{2i} + \beta_4 x_{3i} + \beta_5 x_{4i} + \beta_6 x_{5i} + \varepsilon_i$$

Where μ_i is the number of relapses experienced by patient i from baseline to Week 52, receipt of rescue therapy or death (whichever occurs first), t_i is the total follow up time for patient i, x_{1i} is the randomized treatment for patient i, x_{2i} is the disease type for patient i, x_{3i} indicates whether patient i received immunosuppressive treatment (other than corticosteroids for INS) prior to study entry, x_{4i} is the baseline corticosteroid dose for patient i and x_{5i} is the baseline bodyweight for patient i.

The total number of relapses, total exposure to study treatment (weeks), and rate of relapse will be presented by treatment group along with maximum likelihood estimates for the rate ratio, 95% confidence interval for the rate ratio, and p-value.

A zero inflated negative binomial model will be applied as part of a sensitivity analysis of the modelling assumptions.

Missing Data

The maximum analysis follow-up time to accumulate relapses is 52 weeks, or until the patient withdraws, dies, or receives rescue therapy (other than systemic corticosteroids), whichever occurs first. If a patient withdraws, dies, or receives rescue therapy within 52 weeks, the missing data will not be imputed. In this case, the number of relapses up until the time of study withdrawal, death, or rescue will be used in the analysis. Missing components for the definition of relapse (UPCR assessments at scheduled visits at Weeks 12, 24, 40 and 52, and UPCR assessments triggered by dipstick home monitoring) will be imputed using the following method. If all UPCR assessments for the definition of relapse are missing, non-responder imputation will be implemented i.e., the participant will be considered to have had a relapse. A sensitivity analysis employing worst observation carried forward will be implemented i.e. for missing values, the participant's worst previous value of UPCR will be used in the relapse definition.

Mean Change in CureGN Edema Scale from Baseline to Week 52

- **Variable:** Mean Change in CureGN Edema scale is defined as the mean change in total edema severity (see Section 4.6.6 for derivation of this scale) 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.
- **Strategy for Intercurrent Events:**
  - Hypothetical Strategy will be used to deal with death (i.e., the values of the variables of interests will be imputed by the LOCF method).
  - 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, i.e., the values of the variables of interest measured after the occurrence of this intercurrent event will be used.
- 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.
- **Population Summary Measure:**
  - Difference in adjusted means between obinutuzumab and MMF arms at a specified timepoint of visit.

Mean Change in "General Fatigue" Domain of PedsQL-Multidimensional Fatigue Scale Total Score from Baseline to Week 52

- **Variable:** Mean Change in "General Fatigue" (see Section 4.6.6 for derivation of this scale) domain of PedsQL-Multidimensional Fatigue scale total score is defined as the mean change in the total score of the "General Fatigue" domain of the PedsQL-Multidimensional Fatigue scale 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.

- **Strategy for Intercurrent Events:**
  - See **Mean Change in CureGN Edema Scale from Baseline to Week 52** endpoint.

- **Population Summary Measure:**
  - Difference in adjusted means between obinutuzumab and MMF arms at a specified timepoint of visit.

Mean Change in "Physical Functioning" Domain of PedsQL from Baseline to Week 52

- **Variable:** Mean Change in "Physical Functioning" (see Section 4.6.6 for derivation of this scale) domain of PedsQL is defined as the mean change in the Physical Functioning score on the PedsQL 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.
- **Strategy for Intercurrent Events:**
  - See **Mean Change in CureGN Edema Scale from Baseline to Week 52** endpoint.

- **Population Summary Measure:**
  - Difference in adjusted means between obinutuzumab and MMF arms at a specified timepoint of visit.

Missing Data

Missing data for the above patient reported outcome (PRO) endpoints will be imputed by multiple imputations using data from patients who did not experience any intercurrent event. Missing respective PRO endpoint score at Week 52 will be imputed by FCS predicted mean matching method. A set of candidate donors with 5 members is chosen for the predictive mean matching method. Separate imputation models will be used for each treatment arm. The model will contain the following variables (in order of being imputed):

- Baseline PRO score (CureGN Edema Scale / PedsQL – General Fatigue / PedsQL – Physcial Functioning)
- Disease Type (Stratification factor)
- Prior use of immunosuppressive treatment (other than corticosteroids for INS) (Stratification factor)
- Sex
- Age

- Body mass index (BMI)
- Week 48 PRO score
- Week 52 PRO score

- The imputation will be implemented using the following three standard steps to generate inference from the imputed data. The number of imputations will be set to 100.

  1. **Imputation step**:
     a. The missing data will be imputed 100 times to generate 100 imputed datasets for the patients who did not experience any intercurrent event
     b. Data after the occurrence of first intercurrent event will be imputed separately 100 times as well for the patients who experienced intercurrent events
     c. The two set of imputed datasets will be combined to obtain 100 full datasets each including all the patients in the analysis population
     d. 100 burn in iterations and a seed of 5678234 will be used.
  2. **Analysis step**: Each of the 100 imputed datasets will be analyzed using ANCOVA model
  3. **Pooling step**: The results from the 100 imputed datasets will be combined for inference following the methodology developed by Rubin (Rubin 1987).

The described missing data imputation procedure uses only data from patients who did not experience an intercurrent event. Due to the sample size of this study and the unknown incidence of intercurrent events in this population, subsetting the study population in this manner may make implementing the multiple imputation procedure infeasible, due to a lack of observations. In the event this occurs, the described missing data imputation procedure will be implemented using data from all patients in the study, regardless of whether they experienced an intercurrent event.

Example SAS code which will be used to implement this multiple imputation approach is provided in Appendix 3.

4.3.2 Supportive Secondary Endpoints

For the following analyses no adjustment for multiplicity will be performed; any p-values presented will be nominal and treated as exploratory only.

4.3.2.1 Safety

Safety data (including exposure, laboratory, vital signs and AEs) will be analyzed according to the approach described in Section 4.5.

4.3.2.2 Serum Concentration of Obinutuzumab over Time

Serum concentrations of obinutuzumab will be analyzed according to the approach described in Section 4.6.3.

4.3.2.3 Proportion of Patients Achieving B-cell Depletion (HSFC) over Time

The proportion of patients achieving B-cell depletion in blood (by TBNK and high sensitivity flow cytometry [HSFC]) over time will be analyzed according to the approach described in Section 4.6.4.

4.3.2.4 Total Peripheral B cell and B cell Subsets Counts over Time

The total peripheral B cell and B cell subsets counts in blood will be analyzed according to the approach described in Section 4.6.4.

4.4 EXPLORATORY ENDPOINTS ANALYSIS

[redacted]

4.4.1 Time-to-Event Exploratory Endpoints

[redacted]

4.4.2 Binary Exploratory Endpoints

[redacted]

4.4.3 Continuous Exploratory Endpoints

[redacted]

4.5 SAFETY ANALYSES

All safety analyses will be performed in the safety-evaluable analysis set defined in Section 3, unless otherwise specified, with data collected in the 52 Week open-label treatment period for each patient. Patients will be analyzed according to the treatment they actually received. Patients who were randomized to the study but who did not receive any study drug will not be included in the safety analysis set. Safety outputs will include data until the point of rescue for the patients who receive rescue therapy (excluding systemic corticosteroid rescue). Limited key safety outputs will be produced for post-rescue data.

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

Limited key safety outputs will be produced including data collected after the 52 Week open-label treatment period until the CCOD.

4.5.1 Extent of Exposure

A summary of duration of exposure to study treatment will be produced using the dose recorded on the eCRF. The number of obinutuzumab infusions, treatment duration and total cumulative dose of obinutuzumab over the 52-week open-label treatment period will be summarized. Obinutuzumab treatment duration will be calculated as the difference between the exposure date and date of first dose plus one day, where the exposure date is the earliest of the Week 52 visit or early study withdrawal.

MMF exposure will be summarized using treatment duration and total cumulative dose.

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

4.5.2 Adverse Events

All verbatim AE terms will be coded using the latest version of Medical Dictionary for Regulatory Activities, and AE severity will be graded according to a four-point scale (mild, moderate, severe, life-threatening). In addition, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade will be recorded, if applicable, through use of the NCI CTCAE (v 5.0) grading scale. A listing of serious adverse events (SAEs) caused by a protocol-mandated intervention occurring during screening will be produced.

For safety analyses, unless otherwise specified, only treatment-emergent AEs will be included in the analyses. Treatment-emergent AEs will be defined as any new AEs reported or any worsening of an existing condition on or after post randomization obinutuzumab infusion or MMF administration through the completion of the study or until a patient discontinues the study prematurely. AEs with missing onset date will be considered to be treatment emergent. AEs with partially missing onset date will also be included as treatment emergent when the month (if it was recorded) and the year occur on or later than the month and year of the study treatment start date.

Safety analyses will be performed on the safety-evaluable analysis set as defined in Section 3.

AEs will be summarized by system organ class (SOC) and preferred term (PT), and will be presented in order of descending frequency summed across the treatment arms within each SOC and PT. For each treatment group, the incidence count for each AE PT will be defined as the number of patients reporting at least one treatment-emergent occurrence of the event (multiple occurrences of the same AE in 1 patient will be counted only once). The proportion of patients with an AE will be calculated as the incidence count divided by the total number of patients in the safety-evaluable analysis set. Each table will also present the total number of AEs reported where multiple occurrences of the same AE in an individual are counted separately. For events of varying severity, the highest severity/grade will be used in relevant summaries.

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

- All AEs
- SAEs
- AEs by relationship to study treatment
- AEs leading to study treatment discontinuation
- AEs leading to study treatment modification
- AEs by common terminology criteria grade
- AEs by mild, moderate, severe, or life-threatening as per the investigator's clinical judgment
- Infections
- Serious Infections
- AEs leading to study withdrawal
- Adverse events of special interests (AESIs) as defined in Section 8.3.8 of Protocol
- Disseminated intravascular coagulation
- AEs leading to death

4.5.2.1 Laboratory Data

Relevant laboratory will be displayed by time, with grades identified where appropriate. Summary statistics for the absolute and change from baseline values will be produced by visit and treatment arm for laboratory parameters. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum post-baseline severity grade.

4.5.2.2 Immunoglobulins

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

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

4.5.2.3 Lymphocyte Populations

The absolute values and change from baseline will be summarized by treatment group and visit for $CD3^+$ T-cells, $CD3^+CD8^+$ cytotoxic T-cells, $CD3^+CD4^+$ helper T-cells, and $CD16^+CD56^+$ natural killer cells.

4.5.2.4 Vital Signs

Vital sign (pulse rate, respiratory rate, blood pressure, and temperature) will be displayed by time, with grades identified where appropriate. Changes in vital signs will be summarized.

4.5.2.5 ECGs

Baseline ECG data will be summarized descriptively.

4.6 OTHER ANALYSES

4.6.1 Summaries of Conduct of Study

Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm.

4.6.2 Summaries of Demographics and Baseline Characteristics

Summaries by treatment arm for clinically important demographic and baseline characteristics will be provided. The variables will be summarized using means, standard deviations (SD), medians, and ranges for continuous variables and proportions for categorical variables. The baseline summary will include:

Demographics:

- Age (years)
- Sex
- Height (cm)
- Weight (kg)
- BMI
- Race
- Ethnicity
- Region

Baseline Characteristics:

- Serum creatinine
- eGFR
- UPCR
- Albumin
- Oral corticosteroid usage at study entry (Y/N)
- Disease Type (stratification factor)
- Prior use of immunosuppressive treatment (other than corticosteroids for INS) (stratification factor)

4.6.3 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 vs. efficacy and obinutuzumab exposure vs. safety. Relevant observed relationships between exposure vs. safety parameters and exposure vs. efficacy may be further characterized using different approaches such as logistical regression analyses and indirect response modeling. Results of the population PK, exploratory exposure-response, and PD analyses may be reported separately.

Additional PK and PD analyses may be conducted as appropriate.

4.6.4 Pharmacodynamic Analyses

All PD analyses will be carried out using the safety-evaluable analysis set. The primary PD biomarker will be $CD19^+$ B-cell counts in blood. Total $CD19^+$ B-cell counts via MRB 1.1 (HSFC) and T-, B-, natural killer–cell (TBNK) flow cytometry will be summarized graphically and descriptively over time by treatment group. In addition, the number and proportion of patients with blood CD19+ B cells < LLOQ of MRB 1.1 (as defined by the central lab) and the number and proportion of patients with blood CD19+ B cells below 10 cells /µL via TBNK will be summarized at each timepoint. Counts of individual B cell subsets via BCP2.2 will be summarized graphically and descriptively over time by treatment group. Additionally, the absolute and percent change from baseline for total $CD19^+$ B cells and individual B cell subsets will be computed at each sampling timepoint.

Additional exploratory analyses will be performed to assess the possible relationship between biomarkers in blood and efficacy, clinical parameters, safety, PK, immunogenicity, or other biomarker endpoints.

[redacted]

[redacted]

[redacted]

4.6.6 Clinical Outcome Assessment Analyses

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:

Pediatric Quality of Life Inventory - 4.0 Generic Core Scale (PedsQL)

The Pediatric Quality of Life Inventory 4.0 Generic Core scale 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, items scored from 0 to 4 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)
- 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 (See Appendices A5-2.1 to A5-2.6 of the Protocol).

Pediatric Quality of Life Inventory - Multidimensional Fatigue Scale (PedsQL-Fatigue Scale)

The PedsQL-Multidimensional Fatigue scale 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 5-point Likert response format and transformed to 0–100 total score where a higher score indicates less fatigue. Scoring of individual domains is also possible. The measure takes approximately 5–7 minutes to complete (See Appendices A5-3.1 to A5-3.6 of the Protocol).

Cure Glomerulonephropathy Edema Scale

The Cure Glomerulonephropathy Network (CureGN) Edema scale 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 resulting in a score range of 0-40 (See Appendix A5-4 of the Protocol).

Subject's Global Assessment of Disease Activity

The Subject's Global Assessment of Disease Activity (SGA) 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) (see Appendices A5–5 and A5–6 of the Protocol). 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:

Physician's Global Assessment of Disease Activity

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

4.6.7 Analyses of Subgroups of Interest

No additional subgroup analyses are planned.

4.6.8 Analyses of China Subpopulation

A separate analysis will be performed for the China subpopulation, where available data from all participants enrolled at China sites (during both the global enrollment phase and an extended China enrollment phase, if applicable) will be combined and summarized. Data from any extension to the global enrollment period will not be included in the primary analysis of the main study. Results from the China subpopulation will be summarized in a separate addendum Clinical Study Report (CSR).

All analyses described in this section will include all data from the China subpopulation collected up to the CCOD for the China subpopulation analysis as defined in Section 2.2.

The participant set for the China subpopulation analyses includes all participants enrolled at China sites. All the analysis will be in a descriptive manner and no hypothesis testing will be done. Data for the China subpopulation will be summarized using the same statistical methods as described in Section 4.1-Section 4.5 when data allows.

4.7 INTERIM ANALYSES

4.7.1 Interim Analysis/Analyses

There is no interim analysis planned for this study.

4.8 CHANGES TO PROTOCOL PLANNED ANALYSES

The following changes have been made to the protocol planned analyses:

Key Secondary Endpoint Testing Order (Section 2.1)

The sequence for endpoint testing will be the primary endpoint followed by the key secondary endpoints in the following order:

1. Overall RFS (including all available data at the CCOD) defined as the time from randomization to first relapse or death
2. Cumulative corticosteroid dose from baseline to Week 52
3. Number of relapses from baseline to Week 52
4. Proportion of patients 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 (except for treatment discontinuation for any reason)
5. Probability of RFS at Week 52
6. Proportion of participants experiencing edema-associated relapse during the 52-week treatment period
7. Mean change in CureGN Edema Scale from baseline to Week 52
8. Mean change in "General Fatigue" domain of PedsQL-Multidimensional Fatigue scale total score from baseline to Week 52
9. Mean change in "Physical Functioning" domain of PedsQL from baseline to Week 52

Intercurrent Events and Handling Strategies for Primary Endpoint (Section 4.2.1)

The intercurrent events and their handling strategies for the primary endpoint were updated:

- Treatment discontinuation for any reason will be handled using treatment policy

Intercurrent Event Handling Strategies for Overall RFS (Section 4.3.1.1)

The intercurrent event handling strategies for overall relapse-free survival were updated. Only the intercurrent event of death will be treated as part of the endpoint definition. The variable definition for this endpoint was therefore updated as: "Time from randomization to first relapse or death".

Estimand Properties for The Proportion of Participants in Sustained Complete Remission at Week 76 (Section 4.3.1.2)

The patient population defined within the estimand was updated to "Patients with FRNS or SDNS who were randomized into the study at least 24 weeks prior to the date of randomization for the final patient in the study."

Intercurrent events and their handling strategies were updated to align with the primary endpoint:

- Treatment discontinuation for any reason will be handled using treatment policy

Intercurrent Event Handling Strategies for the Proportion of Participants Experiencing Edema-Associated Relapse during the 52-Week Treatment Period (Section 4.3.1.2)

- All intercurrent events (except death) will be handled using the treatment policy strategy
- Death will be handled using the while-on-treatment strategy

Missing data handling strategy for primary endpoint and secondary binary endpoints (Section 1.1, Section 4.2.2, Section 4.3)

Due to the small number of patients on study and the small amount of missing UPCR data anticipated given UPCR is an objective measure, there were concerns that the proposed multiple imputation approach would encounter convergence issues. As an alternative, simpler approach, a non-responder imputation will be implemented, alongside a tipping point analysis.

5. SUPPORTING DOCUMENTATION

Appendix 1 Psychometric Validation of the PedsQL-Multidimensional Fatigue Scale in INS Patients: Analysis Plan

1 Study 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 (Vivarelli et al. 2017).

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 " (Vivarelli et al. 2017). In the latter 2 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.

Semi-structured interviews with juvenile INS patients indicate a substantial impact of the disease on physical, social, and mental health-related quality of life regardless of age or diagnosis. Physical symptoms that are commonly of primary concern include swelling, fatigue, and pain (see Carlozzi et al.2021).

In the INSHORE study, fatigue was assessed using the PedsQL-Multidimensional Fatigue scale. The associated key secondary endpoint is mean change from baseline at Week 52 in the General Fatigue domain of the PedsQL-Multidimensional Fatigue scale.

2 Objective

1. To establish the reliability, validity, and responsiveness of the PedsQL-Multidimensional Fatigue scale in INS patients to facilitate potential label inclusion.

The PedsQL-Fatigue scale 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). We used 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. Scoring of individual domains is also possible. The measure takes approximately 5-7 minutes to complete.

Data: All data will stem from a single pivotal Phase 3 trial, INSHORE.

3 Analyses to Support Objective 1

3.1 Reliability

Internal Consistency

Internal consistency is an estimate of reliability based on the average correlation between items in a scale. This is represented by calculating Cronbach's alpha.

Calculate Cronbach's alpha using data from the 18 scale items in relation to the total PedsQL-Multidimensional Fatigue scale score at Baseline. Cronbach's alpha ≥ 0.7 suggests reasonable internal consistency. In addition, estimates of lambda 2, 4, and omega will be calculated for comparison.

Test-Retest Reliability

Calculate two-way, mixed effects ICC between total PedsQL-Multidimensional Fatigue scores derived at Baseline and Week 12. Correlations ≥ 0.7 indicate reasonable test-retest reliability.

3.2 Validity

Construct Validity

Assesses the degree to which a scale actually measures the construct it was designed to measure. We will use two estimates of construct validity - convergent validity and discriminant validity.

Convergent Validity

Tests if a scale is correlated with other scales that measure the same or related construct. Calculate Spearman's correlation coefficient and Weighted Kappa between:

- Total PedsQL-Multidimensional Fatigue score and PGA score derived at Baseline
- Total PedsQL-Multidimensional Fatigue score and SGA score derived at Baseline

- Total PedsQL-Multidimensional Fatigue score and PedsQL-Physical Functioning domain score derived at Baseline

Discriminant Validity

Tests if a scale is independent from other scales that measure constructs that differ from the one being considered. Calculate Spearman's correlation coefficient and Weighted Kappa between:

- Total PedsQL-Multidimensional Fatigue score and PedsQL-Social Functioning domain at Baseline

Known Groups Validity

Tests if a scale can differentiate between groups known to differ in terms of a disease category. Patients will be grouped according to predefined proteinuria thresholds (UPCR < 1 g/g, UPCR ≥ 1-1.5 g/g and ≥ 1.5 g/g). ANOVA will be used to test the mean differences in total PedsQL-Multidimensional Fatigue scores between groups. Effect sizes (mean difference/SD) will be calculated for the differences between adjacent groups.

3.3 Responsiveness of PedsQL-Multidimensional Fatigue to Changes in Disease Activity

In this section we evaluate the responsiveness of the total PedsQL-Multidimensional Fatigue score in relation to changes in disease status. For this analysis, we will examine the extent to which important longitudinal changes in PGA are associated with changes in the total PedsQL-Multidimensional Fatigue score. PGA score change will be classified in the following manner:

- "Better" = change score < (mean - 0.5SD)
- "Same" = (mean + 0.5SD) ≥ change score ≥ (mean - 0.5SD)
- "Worse" = change score > (mean + 0.5SD)

ANOVA will be used to compare mean total PedsQL-Multidimensional Fatigue score change between groups. Analyses will be based on Week 52 data.

3.4 Derivation of Minimum Clinically Important Difference (MCID) - A Responder Threshold for Assessing Within-Patient Improvement

In order to derive an MCID for the General Fatigue domain of the PedsQL-Multidimensional Fatigue scale, we will employ the PGA and SGA as anchors. For the purpose of this analysis, an "anchor responder" is defined as a patient satisfying the following conditions at Week 52:

- PGA "Better" = PGA change score < (mean - 0.5SD); and
- SGA "Better" = SGA change score < (mean - 0.5SD)

The General Fatigue domain mean and SD of the population of patients falling into this "anchor responder" category will be derived and used to define an MCID for the domain. The MCID responder for the General Fatigue domain is defined as a patient whose domain change score at Week 52 (from Baseline) is ≥ (mean - 2SD) rounded up to the nearest integer.

The proportion of subjects from each treatment group who have improved by the MCID value or greater between Baseline and Week 52 will be calculated. A chi-square test will be conducted to evaluate the differences.

Appendix 2 Protocol Synopsis

This is the Synopsis of Protocol v3 (version applicable at the time of this SAP).

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

Appendix 3 SAS Code

PRIMARY ENDPOINT ANALYSIS PROCEDURE (AND BINARY KEY SECONDARY ENDPOINTS)

```
ods output CommonPdiff = crr_diffrateci ;
ods output cmh = crr_cmh ;
proc freq data = crr_combined;
        tables strat1*strat2*treatment*crr / missing alpha = 0.05 cmh commonriskdiff(column = 2
cl =newcombe);
run;
```

PRO IMPUTATION PROCEDURE

Imputation (Step 1)
Run PROC MI separately for each planned treatment group of "Obinutuzumab" and "Placebo" to generate 100 imputed datasets for patients who did not experience ICE of death.

```
proc mi data = pro_mi_data out = pro_mi_out seed = 5678234 nimpute = 100 noprint;
      class Sex DiseaseType PriorImmuno;
      FCS nbiter=100 REGPMM(PRO_baseline / k=5);
      FCS nbiter=100 DISCRIM(DiseaseType = PRO_baseline / k=5);
      FCS nbiter=100 DISCRIM (PriorImmuno = DiseaseType  PRO_baseline / k=5);
      FCS nbiter=100 DISCRIM (Sex = PriorImmuno DiseaseType  PRO_baseline / k=5);
      FCS nbiter=100 REGPMM(Age =  Sex PriorImmuno DiseaseType  PRO_baseline / k=5);
      FCS nbiter=100 REGPMM(BBMI = Age Sex PriorImmuno DiseaseType  PRO_baseline /
k=5);
      FCS nbiter=100 REGPMM(PRO_W48 =  BBMI Age Sex PriorImmuno DiseaseType
PRO_baseline / k=5);
      FCS nbiter=100 REGPMM(PRO_W52 = PRO_W48 BBMI Age Sex PriorImmuno
DiseaseType  PRO_baseline / k=5);
      var  PRO_baseline DiseaseType PriorImmuno Sex Age BBMI PRO_W48 PRO_W52;
run;
```

Analysis (Step 2)

- Calculate change from baseline at Week 52 for each PRO endpoint using imputed values for each of 100 multiple datasets.
- For each of 100 multiple datasets add patients who experienced ICE of death (handled using LOCF method) to obtain full datasets including all the patients in the analysis population
- Analyse each of 100 multiple datasets using PROC MIXED to obtain 100 statistical estimates for adjusted mean for each planned treatment group of "Obinutuzumab" and "MMF" and 100 statistical estimates for difference in adjusted means.

```
proc mixed data = pro_combined_data;
      by _imputation_;
      class Treatment DiseaseType PriorImmuno;
      model chg_PRO_W76 = Treatment PRO_baseline DiseaseType PriorImmuno;
      lsmeans treatment / alpha = 0.05 cl pdiff;
      ods output lsmeans = PRO_chg_lsmeans_W76;
      ods output diffs = PRO_chg_diff_W76;
run;
```

Pooling (Step 3)

- 3.1: Use estimates for adjusted mean obtained from PROC MIXED in Step 2 to generate a pooled estimate for adjusted mean for each planned treatment group of "Obinutuzumab" and "MMF" using PROC MIANALYZE. Required standard error is obtained from PROC MIXED in Step 2.

```
proc mianalyze data = PRO_chg_lsmeans_W76;
        by Treatment;
        modeleffects estimate;
        stderr stderr;
        ods output parameterestimates = __mian_ PRO_chg_lsmeans_W76;
run;
```

  The standard error for the adjusted mean is estimated from the above PROC MIANALYZE.

- 3.2: Use estimates for difference in adjusted means obtained from PROC MIXED in Step 2 to generate a pooled estimate for difference in adjusted means using PROC MIANALYZE. The required standard error is obtained from PROC MIXED in Step 2.

```
proc mianalyze data = PRO_chg_diff_W76;
        by Treatment;
        modeleffects estimate;
        stderr stderr;
        ods output parameterestimates = __mian_ PRO_chg_diff_W76;
run;
```

  The 95% CI for difference in adjusted means and p-value are estimated from the above PROC MIANALYZE.

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