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LNP023

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A randomized, open-label, two arm, parallel group, proof-of-concept clinical trial to investigate the efficacy and safety of LNP023 compared with rituximab in the treatment of subjects with idiopathic membranous nephropathy

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study procedures. Note: The SOM will not be a part of the Clinical Study Report.

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List of abbreviations

ACEi	Angiotensin Converting Enzyme inhibitor
AE	adverse event
aHUS	Atypical hemolytic uremic syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AP	Alternative Pathway
ARB	Angiotensin II Receptor Blocker
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
b.i.d.	twice a day
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BP	Blood Pressure
BUN	blood urea nitrogen
C3G	C3 Glomerulopathy
CDRD	complement-driven renal diseases
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
cm	Centimeter
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COVID-19	Coronavirus Disease 2019
CRF	Case Report/Record Form (paper or electronic)
CSR	Clinical study report
CV	coefficient of variation
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DMC	Data Monitoring Committee
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ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	estimated Glomerular Filtration Rate
ELISA	Enzyme-linked immunosorbent assay
eSource	Electronic Source
ESRD	End Stage Renal Disease
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FAS	Full Analysis Set
FB	Factor B
FiH	First in Human
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GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
h	Hour

HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HBVsAg	HBV surface antigen
hCG	human Chrorionic Gonadotropin
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	human immunodeficiency virus
i.v.	Intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IG	Immunoglobulin
IgAN	Immunoglobulin A Nephropathy
IgG	Immunoglobulin G
IgM	Immunoglobulin M
iMN	Idiopathic Membranous Nephropathy
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine system
KDIGO	Kidney Disease: Improving Global Outcomes
KDQoL	Kidney Disease Quality of Life
kg	Kilogram
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
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MAD	Multiple Ascending Dose
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MMF	Mycophenolate mofetil
MMRM	Mixed effect Model Repeat Measurement
MN	Membranous Nephropathy
NGAL	Neutrophil Gelatinase-Associated Lipocalin
NOAEL	No Observed Adverse Effect level
NSAID	Nonsteroidal anti-inflammatory drug
p.o.	Oral

PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PLA2R	Phospholipase A2 Receptor
PNH	Paroxysmal Nocturnal Hemoglobinuria
PRO	Patient Reported Outcomes
PT	prothrombin time
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
RBC	red blood cell(s)
RU	Relative Unit
SAD	Single Ascending Dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic Blood Pressure
sC5b-9	Soluble C5b-9
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SOM	Site Operations Manual
SOP	Standard Operating Procedures
SRBC	Sheep red blood cell
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	Tuberculosis
TBL	Total Bilirubin Level
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UA	Urine Albumin
UACR	Urine Albumin Creatinine Ratio
ULN	upper limit of normal
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UP	Urine Protein
UPCR	Urine Protein Creatinine Ratio
WHO	World Health Organization
γ-GT	Gamma-Glutamyl Transpeptidase

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last subject or at a later point in time as defined by the protocol
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
eSource	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug/treatment	The drug whose properties are being tested in the study
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest
Personal Data	This include subject's name, initials, address, gender, age/date of birth, health information, study samples and medical images (images of medical biopsies).
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Run-in Failure	A subject who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to subject's medications or other intervention)
Screen Failure	A subject who is screened but is not treated or randomized

Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Study treatment	Any drug or combination of drugs administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent (WoSC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data.

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Protocol summary

Protocol number	LNP023D12201
Full Title	A randomized, open-label, two arm, parallel group, proof-of-concept clinical trial to investigate the efficacy and safety of LNP023 compared with rituximab in the treatment of subjects with idiopathic membranous nephropathy
Brief title	Efficacy and safety of LNP023 compared with rituximab in subjects with idiopathic membranous nephropathy
Sponsor and Clinical Phase	Novartis Institutes for BioMedical Research / Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to ascertain the efficacy, safety, tolerability and pharmacokinetics of LNP023 over a 24-week treatment period compared with rituximab in subjects with idiopathic membranous nephropathy (MN). The primary endpoint of the study will be the ratio between baseline Urine Protein Creatinine Ratio (UPCR) and UPCR at 24 weeks of treatment (from 24h urine collection). The study will target subjects with idiopathic MN at high risk of disease progression, on the basis of serum anti-PLA2R antibody titer and high-grade proteinuria.
Primary Objective(s)	To assess the efficacy of LNP023 compared with rituximab
Secondary Objectives	Objective 1: To assess the safety and tolerability of LNP023 Commercially Confidential Information Objective 3: To assess the effect of LNP023 compared with rituximab on proteinuria remission and renal function Objective 4: To assess the pharmacokinetics of LNP023

Study design	This is a randomized, open-label, two arm, parallel group, proof-of-concept, non-confirmatory study evaluating the efficacy and safety of LNP023 compared with rituximab in subjects with MN who are at high risk of disease progression defined on the basis of antibody anti-PLA2R titer (≥60 RU/mL) and proteinuria (≥3.5 g/24h). The screening period will last up to 12 weeks and the whole study will last up to 65 weeks. Approximately 52 subjects will be randomized in the study. Treatment with LNP023 or rituximab is open label for subjects, investigators and sponsor. Commercially Confidential Information Efficacy will be evaluated at the end of the 2 week treatment period. The randomization ratio is 1:1; LNP023: rituximab.
Population	Approximately 52 subjects (male or female, 18 years old or older, with a biopsy proven MN, will participate in this study.
Key Inclusion criteria	• Female or male adult (≥18 years) subjects at screening visit with a diagnosis of idiopathic (primary) MN confirmed by renal biopsy within 36 months prior to screening. A renal biopsy may be taken at any time during the run-in period to confirm the diagnosis of MN and facilitate subject eligibility, if the most recent biopsy was performed greater than 36 months prior to the screening visit. • Anti-PLA2R antibody titer of ≥ 60 RU/mL at screening visit (based on the EuroImmun ELISA test) • Urine protein ≥3.5 g/24h at run-in and baseline visits • ≤50% reduction in both anti-PLA2R level and 24h urine protein between first measurement at screening or run-in visit and baseline • Estimated GFR (using the CKD-EPI formula) ≥30 mL/min per 1.73 m^2 at screening visit • Receiving stable dose at the maximum recommended dose according to local guidelines or maximum tolerated dose of ACEi and/or ARB and/or statins and/or diuretics for at least 8 weeks prior to Day 1 • Vaccination against *Neisseria meningitidis, Streptococcus pneumoniae* and *Haemophilus influenzae* (in accordance with local guidelines) at least 28 days prior to Day 1 and no longer than 5 years prior to Day 1

Key Exclusion criteria	• Secondary causes of MN, e.g. systemic autoimmune diseases, solid or hematological malignancies, infections or chronic intake of drugs (e.g. gold salts, NSAIDs, penicillamines) • Diagnostic renal biopsy showing evidence of crescent formation in glomeruli, suggestive of an alternative or additional diagnosis to primary idiopathic MN • Previous treatment with B-cell depleting or B-cell modifying agents such as, but not limited to rituximab, belimumab, daratumumab or bortezomib • Previous treatment with immunosuppressive agents such as cyclophosphamide, chlorambucil, mycophenolate mofetil (or equivalent), cyclosporine, tacrolimus or azathioprine within 90 days prior to Day 1. Low dose systemic corticosteroid therapy is permitted, though the subject should have been on stable dose equivalent to ≤10 mg prednisolone for at least 90 days prior to Day 1 • Previous treatment with gemfibrozil or strong CYP2C8 inhibitors such as clopidogrel within 7 days prior to Day 1 • Presence or suspicion (based on judgment of the investigator) of active infection within 30 days prior to Day 1, or history of severe recurrent bacterial infections • Known contraindications for the use of rituximab, including hypersensitivity to the active substance or to murine proteins, or to any of the excipients (sodium citrate, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid, water for injections). Other contra-indications for the use of rituximab, including active, severe infection, patients in a severely immunocompromised state, severe heart failure (NYHA Class IV) or severe, uncontrolled cardiac disease
Study treatments	Test treatment: LNP023 CCI 200 mg b.i.d. Reference treatment: rituximab 1 g (two intravenous infusions)
Efficacy assessments	Ratio between baseline UPCR and UPCR at 24 weeks of treatment (from 24h urine collection) UPCR measured in first morning void urine Proportion of subjects with a complete remission, defined as proteinuria ≤0.3 g/day at 24 weeks of treatment, derived from 24h urine collection Proportion of subjects with a partial remission, defined as reduction of urine protein from baseline ≥50% plus final urine protein level ≤ 3.5 g/24h but >0.3 g/24h derived from 24h urine collection Change in eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation from baseline to 24 weeks of treatment
Pharmacodynamic assessments	Plasma levels of Bb and sC5b-9

Pharmacokinetic assessments	Non-compartmental parameters in plasma related to total parent drug, including, but not limited, to Tmax, Cmax, AUClast and AUCtau will be calculated for each dose level. Urine: renal plasma clearance derived from 24h urine at week 16.
Key safety assessments	ECG, vital signs, safety laboratory data, physical exam and collection of AEs assessed from baseline until the end of study visit.
Other assessments	Commercially Confidential Information
Data analysis	The primary aim of the study is to assess the reduction in UPCR (measured in 24h urine) in LNP023 treated subjects compared with subjects treated with rituximab after 24 weeks of treatment. To assess the primary objective, UPCR (log-transformed ratio of UPCR at week 24 vs baseline) will be analyzed using a mixed model for repeated measures. The results will be back transformed and presented on the original scale. The model will include treatment group (LNP023 200 mg, rituximab), timepoint (as study day relative to start of study treatment, i.e. Day 113 and Day 169) Commercially Confidential Information Baseline is defined to be the last measurement prior to first dosing. Treatment group by timepoint and timepoint by baseline will be included as interaction terms. Timepoint will be included as a repeated factor with an unstructured covariance matrix to allow adjustment for correlations between timepoints within patients. The intercurrent event considered for this analysis is early treatment discontinuation. For this intercurrent event, data from subjects who have discontinued treatment early will be regarded as missing after the discontinuation. The difference between LNP023 200 mg and rituximab in change from baseline in log-transformed UPCR will be estimated from the model and presented with 95% confidence intervals. Simpler models will also be considered in case the pre-specified model does not fit the data well. The following two criteria will be used to assess treatment efficacy: • Statistically significant decrease (no worse than 55% increase) in UPCR at week 24 visit in LNP023 200 mg -treated subjects vs. rituximab-treated subjects at one-sided 10% level (i.e. H_0 = (ratio from BL in UPCR_LNP)/ (ratio from BL in UPCR_Ritux) ≥ 1.55)

	• Estimated mean reduction in UPCR in LNP023 200 mg -treated subjects better than 10% increase vs rituximab-treated subjects (i.e. (ratio from BL in UPCR_LNP)/ (ratio from BL in UPCR_Ritux) < 1.1)
Key words	Idiopathic membranous nephropathy, MN.

1 Introduction

1.1 Purpose

The purpose of this study is to ascertain the efficacy, safety, tolerability and pharmacokinetics of LNP023 over a 24-week treatment period compared with rituximab in subjects with MN.

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The primary end point of the study will be the ratio between baseline Urine Protein Creatinine Ratio (UPCR) and UPCR at 24 weeks of treatment (from 24h urine collection). The study will target subjects with idiopathic MN at high risk of disease progression, on the basis of serum anti-PLA2R antibody titer and high-grade proteinuria.

1.2 Background

Idiopathic (primary) membranous nephropathy (MN) is a glomerular disease in 40-70 year old adults very frequently associated with nephrotic syndrome and significant morbidity, including the progressive loss of renal function leading to End Stage Renal Disease (ESRD). The estimated prevalence is around 550 per million (McGrogan et al 2011; Wetmore et al 2016), giving a total of approximately 100,000 patients in the US and about twice that in the EU. There is also evidence that the prevalence of MN is increasing in certain regions, for example in China (Tang et al 2017).

Diagnosis of MN is made by renal biopsy which shows characteristic membranous thickening of the glomerular basement membrane associated with sub-epithelial deposits of immunoglobulin IgG4 and membrane attack complex (C5b-9) (Fogo et al 2015).

Among patients with MN, 80% present with nephrotic syndrome (a combination of albuminuria ≥ 3 g/24h, hypoalbuminemia, edema, and hypercholesterolemia), which if persistent, results in 40-50% of these patients progressing to ESRD over 10 years. The rate of progression depends on the level of albuminuria; levels ≥ 5 g/24h have decreases in estimated glomerular filtration rate (eGFR) of about 5 mL/min/1.73m2 per year. MN patients may have spontaneous remissions and relapses during the course of disease. About 20% have complete spontaneous remissions of the nephrotic syndrome (to micro-albuminuric levels) and 15% have partial spontaneous remissions (50% reduction in albuminuria to subnephrotic albuminuric levels). Complete remissions, whether spontaneous or treatment induced, are noted to significantly reduce the risk of progression to ESRD. Partial remissions also slow down disease progression, but to a lesser degree (Thompson et al 2015). Both types of remissions primarily occur in the first 1-3 years after diagnosis and are more common when patients are taking an Angiotensin Converting Enzyme inhibitor (ACEi) or Angiotensin Receptor Blocker (ARB) (Cattran and Brenchley 2017; Cattran et al 2017).

Current recommended therapies (KDIGO 2012) include the Ponticelli regimen (oral and i.v. corticosteroids and alkylating agents) or calcineurin inhibitors, though both of these are associated with significant adverse effects. There is increasing use of the B-cell depleting monoclonal antibody rituximab based upon the results of two recent randomized controlled trials (Fervenza et al 2015; Dahan et al 2017), though this agent is not licensed for this indication and does not feature in any current treatment guidelines.

Over 80% of cases of primary idiopathic MN are mediated by nephritogenic autoantibodies against the PLA2 receptor, expressed on the glomerular podocyte, resulting in immune complex formation in the glomerulus. There seems to be a strong correlation between disease progression in MN and auto-antibodies against phospholipase A2 receptor (PLA2R) and patients with high anti-PLA2R antibody levels are less likely to have a spontaneous remission (Pourcine et al 2017). Most autoantibodies against PLA2R are of the IgG4 subclass (Acevedo Ribó et al 2016; Lönnbro-Widgren et al 2015; Yang et al 2016) which have low ability to activate complement through the classical pathway (Borza 2016). However, it is well established that complement is activated in MN as reflected by C5b-9 expression in renal biopsies and by soluble C5b-9 (sC5b-9) levels in urine that correlate with disease progression (Borza 2016; Cybulsky et al 1986; Endo et al 2004; Ma et al 2013; Salant et al 1980). Moreover, animals depleted in C6 (thereby prevented from forming C5b-9 complexes) are protected from proteinuria in experimental MN (Baker et al 1989). Most evidence as reviewed by Borza, suggest a major role of the complement alternative pathway (AP) in MN (Borza 2016). Their further study showed that Factor B (an essential component of the AP) knockout mice (Cfb-/-) did not develop proteinuria nor exhibit glomerular deposition of C3c or C5b-9. Albuminuria was also reduced but not completely abolished in C5-deficient mice, providing the first direct evidence that the AP, especially Factor B, is necessary for pathogenic complement activation by glomerular subepithelial immune complexes and is, therefore, a key mediator of proteinuria in experimental MN (Luo et al 2018).

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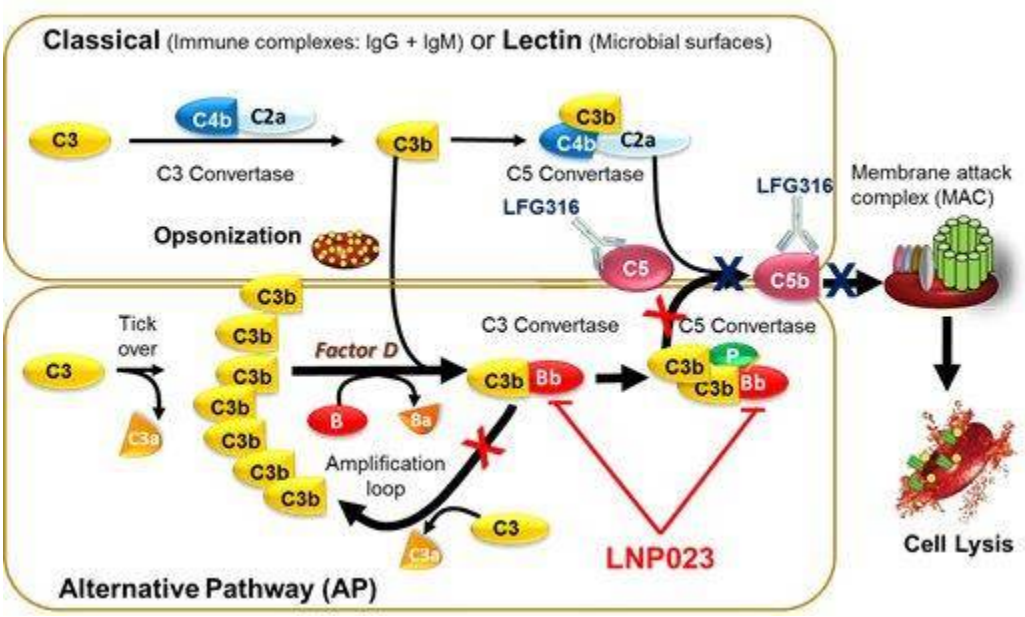
The complement system with its three activation pathways (classical pathway (CP), lectin pathway (LP) and alternative pathway (AP)) and the effect of LNP023 are illustrated in Figure 1-1.

Figure 1-1 Overview of the complement system with and the site of action of LNP023



The figure illustrates how all three complement pathways (CP, LP and AP) converge to the C5 convertase and the terminal pathway to form MAC that will induce lysis of the target cells.

A large number of complement-driven diseases have been identified. Most of these diseases are related to dysregulation of the AP, while other conditions are more dependent upon hyperactivity of the classical (CP) or the lectin pathways (LP). Although eculizumab, which blocks complement C5, is registered for the treatment of paroxysmal nocturnal haemoglobinuria (PNH) and atypical hemolytic uremic syndrome, there are limited therapies available to treat most complement-driven renal diseases (CDRD), which often progress to chronic kidney disease and ESRD. There is a high-unmet medical need for new therapies to treat CDRD including MN and therapies targeting the complement system represent a promising approach.

LNP023 is currently being developed for use in PNH and C3 glomerulopathy (Nester and Smith 2013), two rare diseases in which dysregulation of the complement AP is central in the disease pathogenesis. The compound is also currently being investigated in a Phase 2 study in IgAN (Maillard et al 2015), another renal disease in which the complement system is known to be dysregulated.

FB is an essential component of the AP; blockade of the AP through FB inhibition is expected to be therapeutically beneficial in CDRD through improvement in renal morphology and function and prevention of further disease progression (Kościelska-Kasprzak et al 2014). LNP023 may provide a valid therapeutic approach via a new mechanism of action, which could fill an unmet medical need for patients with CDRD.

Additional activation of the complement system contributes significantly to ongoing glomerular injury; the majority of the current evidence supports involvement of the alternative and lectin pathways, with minimal classical pathway involvement.

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Given the absence of a well-tolerated efficacious therapy for this disorder, there is a strong case for investigating the potential efficacy of LNP023 as an agent to reduce glomerular injury, through inhibition of the complement alternative pathway. Our hypothesis is that complement inhibition will reduce ongoing glomerular inflammation and resultant glomerulosclerosis, reducing the rate of deterioration in kidney function.

Comprehensive information is available in the Investigator Brochure.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the efficacy of LNP023 compared with rituximab	• Ratio between baseline UPCR and UPCR at 24 weeks of treatment (from 24h urine collection)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the safety and tolerability of LNP023	• ECG parameters, vital signs, safety laboratory data, physical exam and collection of AEs assessed from baseline until the end of the study visit.
Commercially Confidential Information	• Plasma levels of Bb and sC5b-9
	• UPCR measured in first morning void
	• Non-compartmental parameters related to drug exposure
• To assess the effect of LNP023 compared with rituximab on proteinuria remission and renal function	• Proportion of subjects with a complete remission, defined as proteinuria ≤0.3 g/day at 24 weeks of treatment, derived from 24h urine collection
	• Proportion of subjects with a partial remission, defined as reduction of proteinuria from baseline ≥50% plus final UP ≤ 3.5 g/24h but >0.3 g/24h at 24 weeks of treatment, derived from 24h urine collection.
	• Change in eGFR applying the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation from baseline to 24 weeks of treatment
• To assess the pharmacokinetics of LNP023	• Plasma: non-compartmental parameters in plasma related to total parent drug, including, but not limited, to Tmax, Cmax, AUClast and AUCtau will be calculated for each dose level.
	• Urine: renal plasma clearance derived from 24h urine at week 16.

Objective(s)	Endpoint(s)
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**

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3 Study design

This is a randomized, open-label, two arm, parallel group, proof-of-concept, non-confirmatory study evaluating the efficacy and safety of LNP023 compared with rituximab in subjects with MN at high risk of disease progression defined on the basis of anti-PLA2R antibody titer (≥ 60 RU/mL) and proteinuria (≥ 3.5 g/24h) (please refer to protocol Section 5.1 for details).

A total of approximately 52 subjects will be randomized into the study: approximately 24 on LNP023 200 mg, approximately 24 on rituximab Commercially Confidential Information

Treatment with LNP023 or rituximab is open label. Commercially Confidential Information

Efficacy will be evaluated at the end of the 24-week period. The randomization ratio is 1:1 (LNP023: rituximab).

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24h urine samples will be collected by the subject at home on the morning of the day prior to the indicated study visit and brought to the study site on the day of visit: samples will be collected 1) at run-in, 2) for baseline, 3) between Day 112 and Day 113, and 4) between Day 168 and Day 169 (end of treatment).

First morning void samples for monitoring of UPCR and other safety urine parameters will be collected 11 times by the subject at home: 1 time at run-in, 1 time for baseline, 7 times during the treatment period and 2 times during safety follow-up.

Pharmacokinetics, safety and other assessments will be conducted according to the study schedule (see Section 8). Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry and urinalysis), adverse event and serious adverse event monitoring.

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Total study duration from screening until end of study (EOS) is approximately 65 weeks.

The study includes (see Figure 3-1):

- a screening visit
- a run-in period of up to 12 weeks
- a baseline visit
- Day 1 (day of first investigational drug administration)
- a treatment period of 24 weeks
- a follow-up period without any treatment of 29 weeks, including the EOS visit

Screening period

The screening period lasts up to 12 weeks and comprises a screening visit, a run-in period that includes up to two visits, and a baseline visit to confirm subject eligibility. After signing the informed consent form and completing initial screening procedures, subjects will enter the run-in period. During the run-in period, all subjects should be vaccinated against *Neisseria meningitidis, Streptococcus pneumoniae* and *Haemophilus influenzae* according to local guidelines. Vaccination should be completed at least 28 days prior to Day 1 (commencement of study treatment). If required, the run-in period can be extended to respect local guidelines regarding the timing for last vaccination dose and start of investigational drug. In case of previous vaccinations more than 5 years before Day 1, a booster dose should be administered according to local guidelines. Antibiotic prophylaxis (including tuberculosis prophylaxis) may be given at the investigator's discretion as per local guidelines.

A renal biopsy may be taken at any time during the run-in period to confirm the diagnosis of MN diagnosis and facilitate subject eligibility, if the most recent biopsy was performed more than 36 months prior to the screening visit.

Subjects will remain on their supportive therapy, e.g. ACEi and/or ARB and or systemic corticosteroids, with or without diuretics, statins or antihypertensive therapy(ies) for the duration of the trial. To be commenced on randomized treatment, subjects must have been on stable therapy with an ACEi and/or ARB, defined as <25% dose change over at least 8 weeks at the maximally tolerated dose (KDIGO 2012) and, if used as part of local standard of care, systemic corticosteroids at a stable dose that does not exceed the equivalent of 10 mg prednisolone daily over at least 90 days prior to Day 1. If dose adjustments of ACEi/ARB or systemic corticosteroids are required, the run-in period may be extended to ensure stable medications as stated above (8 weeks or 90 days respectively). During the treatment period, no change in the dose of these medications is allowed except for safety reasons.

At baseline, laboratory tests, collection of first morning void urine and 24h urine will be performed. To minimize the number of subjects likely to undergo spontaneous disease remission from entering the study and potentially biasing the results through over-representation in any of the study arms, those subjects in whom the 24h urine protein level or anti-PLA2R antibody titer fall by more than 50% compared to first measurement at screening or run-in visit, and those in whom the 24h urine protein level has fallen below 3.5g/24h will be considered a baseline failure and will not proceed to receive any study drug. Baseline period can be extended in case of delays in receiving the anti-PLA2R results.

Subjects are randomized on Day 1 or up to 4 days before, only after eligibility is confirmed, to LNP023 or rituximab.

Treatment period (subjects randomized to theLNP023 treatment arm)

Treatment period lasts for 24 weeks from Day 1 to Day 169:

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Treatment period (subjects randomized to the rituximab treatment arm)

- Day 1 and Day 15: a dose of rituximab 1 g by intravenous infusion (i.v.), will be administered (refer to Section 6.1.1 for more details).
- Subjects should receive pre-medication consisting of an anti-pyretic and an antihistamine (e.g. paracetamol and diphenhydramine) before each dose as per local standards. Where a single dose of glucocorticoid (e.g. methylprednisolone or hydrocortisone) is used in addition to these measures as part of local standard of care, then this is permitted.
- Treatment period will continue till Day 169 without any further rituximab administration.

Safety follow-up and EOS

A safety follow-up period of 29 weeks will follow the treatment period. A call should be performed 30 days after the last day of the treatment period (Day 199, week 28), and a study visit will be performed on Day 266 (Week 37). Subjects may be treated according to local standard of care throughout this follow-up period. All treatments administered should be documented in the study Case Report Forms.

An EOS visit is scheduled on Day 378 (week 53).

Please refer to Section 8 for details regarding assessments to be performed.

4 Rationale

4.1 Rationale for study design

Table 4-1 Rationale for study design

Study Design Aspect	Rationale
Study design	The design of the study addresses the primary objective of assessing efficacy in terms of the reduction of proteinuria in subjects with MN and takes into account the rarity of this disease and the objective nature of the measurement. The parallel design Commercially Confidential Information allows direct comparison between the LNP023 arm and the rituximab arm. Commercially Confidential Information Furthermore, the B cell depletion induced by rituximab would likely be evident upon review of blood count results, thus unblinding the study to investigators. The study has an objective end-point of proteinuria which is difficult to be influenced through knowledge of treatment allocation. For these reasons, a decision was made to perform an open-label study between LNP023 and rituximab.
Targeted study population	The rationale for including subjects with ≥3.5 g/24h of proteinuria and a high titer of anti-PLA2R antibodies (≥60 RU/mL) is that these subjects are potentially at increased risk of progression towards ESRD and generally have a lower rate of development of spontaneous remission. Whilst no absolute anti-PLA2R antibody titer cut-off level has been identified, antibody titers >20 RU/mL are considered clearly positive and higher titers have been reported to be an independent risk factor for not achieving remission of proteinuria (Hoxha et al 2014; Timmermans et al 2015). Enrichment for these subjects will increase the likelihood to detect a treatment-specific effect as the proportion of subjects undergoing spontaneous remission is expected to be lower than in the general MN population. The study design incorporates two strategies to reduce the possibility of subjects likely to enter spontaneous remission from receiving treatment with LNP023 or rituximab. Firstly, as described above, the inclusion criteria stipulate that subjects must have an anti- PLA2R titer ≥60 RU/mL (i.e., 3-fold higher than the EuroImmun assay positive threshold) as well as nephrotic proportion proteinuria. Secondly, all subjects will undergo measurement of both 24h urine protein excretion and anti-PLA2R titer at the beginning of the run-in and at baseline. Subjects in whom there is a >50% reduction in either, or where the urine protein excretion at baseline has fallen below 3.5g/24h, suggesting possible early spontaneous remission, will be considered a baseline failure and will not be commenced on study drug.

Study Design Aspect	Rationale
	Subjects with secondary MN have been excluded from this study as the treatment of this group of disorders differs significantly from primary MN, with a focus on treatment of the underlying disorder.
Randomization	Subjects will be randomized in order to avoid bias in the assignment of treatment groups. The randomization ratio is 1:1;CCI200mg LNP023 to 1 g rituximab. The randomization approach of 1:1 amongst the two arms decreases the chance of an imbalance in subject characteristics between groups, thereby facilitating an unbiased assessment of safety and tolerability. Commercially Confidential Information
Choice of comparator	Rituximab was chosen reference treatment because whilst not currently registered for use in idiopathic membranous nephropathy, rituximab is being used with increasing frequency in a large number of centers and in countries all over the world following an increase in the understanding of the central role of anti-PLA2R antibodies in the disease pathogenesis and the results of the GEMRITUX and MENTOR studies (Fervenza et al 2015; Dahan et al 2017). Furthermore, it was felt that there would be great potential of the likely unacceptability to both subjects and investigators of a two-month run-in period followed by a six month period of placebo treatment in this disorder.
Duration of study periods	Previous studies of anti-PLA2R positive MN; e.g., MENTOR, GEMRITUX (Fervenza et al 2015; Dahan et al 2017) have shown that the response time to complete or partial resolution of proteinuria for treatments e.g. rituximab, calcineurin inhibitors is at least 6 months. However, significant reductions in proteinuria are observed at earlier time-points. The study duration of 6 months was selected to be long enough to ensure that any likely efficacy signal was not missed. The 6-month follow-up period at the end of the study will generate important information about the persistence and duration of any effect on proteinuria reduction.

4.1.1 Rationale for choice of background therapy

Subjects will receive background therapy with maximally tolerated doses of ACEi / ARB in accordance with KDIGO guidelines (KDIGO 2012). The use of these agents is standard of care for subjects with heavy proteinuria to minimize urine protein excretion and to control blood pressure. As change in proteinuria is the primary outcome measure for this study, the dose of ACEi/ARB must remain constant throughout the run-in period (at least 8 weeks prior to Day 1) and the subsequent randomized treatment period.

Additional antihypertensive agents should be used to maintain the blood pressure (BP) within the recommended range (<130/80 mmHg) throughout the run-in period and period of randomized therapy (KDIGO 2012). Where BP rises and the patient is receiving a maximally tolerated dose of ACEi/ARB, this should be controlled with the use of non ACEi/ARB antihypertensive agents. Diuretics and statins may be used as per local standard of care.

Subjects may receive low dose corticosteroid therapy as part of standard of care. The dose must be stable and not exceed the equivalent of prednisolone 10 mg daily over at least 90 days prior Day 1.

4.2 Rationale for dose/regimen and duration of treatment

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The dose regimen for rituximab was selected to be 1g by intravenous infusion on Days 1 and 15. Whilst unregistered in this indication, this is the regimen used most frequently in clinical practice (NHS Commissioning through Evaluation 2019), and was the regimen selected for the MENTOR study (Fervenza et al 2015). A pilot study conducted by the MENTOR study participants investigated whether 4 weekly doses of 375 mg/m^2 resulted in more effective B -cell depletion and a higher remission rate while still maintaining the same safety profile as patient treated with two doses of 1g (Fervenza et al 2015). Twenty patients with MN and proteinuria >5 g/24h received rituximab (4 x 375 mg/m^2) with retreatment at 6 months regardless of proteinuria response. Of the 18 patients who completed 24 month follow-up, 4 had complete remission, 12 partial remission and 2 did not respond. One patient relapsed following a complete remission. Serum rituximab levels using the 4 dose regimen were similar to that obtained with two doses of rituximab. The study authors concluded that four doses of rituximab did result in more effective B cell depletion, however proteinuria reduction at 12 months was basically identical to the results obtained using rituximab 1g on days 1 and 15. Adverse effects noted were mainly infusion-related reactions and none were serious.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Whilst the incorporation of a placebo arm and treatment-blinding of the study would provide the highest quality information on the true overall effect of LNP023, this was discounted because of the likely unacceptability to both subjects and investigators of a screening period followed by a six-month period of placebo treatment in this disorder. The reference treatment rituximab was therefore chosen. Although not currently registered for use in idiopathic membranous nephropathy, nor recommended in international treatment guidelines (KDIGO 2012), the use of rituximab is becoming increasingly prevalent and has been investigated and shown to have encouraging results in both the MENTOR and GEMRITUX randomized controlled studies (Fervenza et al 2015; Dahan et al 2017). The GEMRITUX study reported complete or partial remission in 35.1% (95% CI 19.7 – 50.5%) of rituximab-treated patients compared with 21.1% (8.1 – 34%) receiving supportive care alone. In the UK, use of this agent is being further investigated in idiopathic membranous nephropathy through the NHS Commissioning Through Evaluation program, where data will be collected on approximately 180 patients treated with this agent over 3 to 4 years.

4.4 Purpose and timing of interim analyses/design adaptations

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4.5 Risks and benefits

LNP023 has not previously been administered with therapeutic intent to subjects with MN. Therefore, no statement can be made at this time regarding the actual clinical benefits of LNP023 in this patient population. However, given the mechanism of LNP023, targeting the complement alternative pathway as described in the background section (Section 1.1), there is sound rationale to believe that a therapeutic response can be achieved with the compound in MN subjects.

The risk to subjects in this study will be minimized by adherence to the eligibility criteria and study protocol, close clinical monitoring and guidance for the investigators in the LNP023 IB and in the rituximab SmPC/local country label.

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There may be unknown risks of LNP023, which may be serious, however there have been no events reported to date which qualify as serious adverse drug reactions to LNP023.

Rituximab is not registered for use in idiopathic membranous nephropathy, however has been extensively investigated in the MENTOR and GEMRITUX studies (Fervenza et al 2015; Dahan et al 2017). Please refer to the SmPC/local country label for detailed information regarding rituximab adverse effects.

The GEMRITUX study reported complete or partial remission in 35.1% (95% CI 19.7 – 50.5%) of rituximab-treated patients compared with 21.1% (8.1 – 34%) receiving supportive care alone. There are a number of key risks associated with the use of rituximab as indicated by a Black Box Warning. These are outlined in Section 4.5.3 below. In the GEMRITUX study, 5/37 rituximab-treated patients and 4/38 supportive care-treated patients developed serious adverse events. Only one SAE was considered related to the administration of rituximab in a patient who developed prostatitis, with a favorable long-term outcome. No rituximab-treated patients developed leucopenia. Infusion-related reactions were avoided through the routine use of premedication with solumedrol, paracetamol and dexchlorpheniramine.

4.5.1 Blood sample volume

A volume of blood smaller than that typically collected at a blood donation session is planned to be collected over a period of about 65 weeks from each subject as part of the study. In the LNP023 arm up to 400 mL will be collected during the whole study. In the rituximab arm, up to 330 mL of blood will be collected. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the Assessment Schedules (Table 8-1 and Table 8-2).

A summary blood log is provided in the Site Operations Manual (SOM). Instructions for all sample collection, processing, storage and shipment information is also available in the SOM and in central laboratory manual.

See Section 8.5.3.1 regarding the potential use of residual samples.

4.5.2 Potential safety risk for LNP023

CCI potential safety risks have been identified, namely 'infections',

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Infections

LNP023 blocks FB and thereby the AP, which is important for the defense against microbes. The immunological response to infections is therefore likely to be blunted. Thus, patients with mutations of FB are generally healthy, but have impaired resistance against bacterial infections (Slade et al 2013). Complement is particularly important for the destruction of encapsulated bacteria such as *N. meningitidis, S. pneumoniae* and *H. influenzae*. The annual incidence of invasive infections with *N. meningitidis* is between 0.1-2.0 cases per 100,000 with great variation between regions (Sridhar et al 2015). For *S. pneumoniae* the annual risk is 4 cases per 100,000 in individuals between 18 and 35 years of age, but the risk is higher for small children and for the elderly (35 cases per 100,000 for individuals <2 or >65 years) (Alanee et al 2007). For *H. influenzae* the annual incidence is 1.6 per 100,000 in the US (MacNeil et al 2011). To mitigate the risk, all subjects must be pre-vaccinated against *N. meningitidis, S. pneumoniae* and *H. influenzae*. Furthermore, patients will be closely monitored for signs and symptoms of infection. Patients will be instructed to contact the investigator if they suspect infection/experience potential symptoms of infection between visits.

High antibody titers are achieved at Day 28 after a single injection of vaccine against *N. meningitidis* (Gossger et al 2012; Keyserling et al 2005). Similar effects are seen with the vaccines against *S. pneumoniae* (Bryant et al 2015; McFetridge et al 2015). In all of these publications, immune response was only measured at least 4 weeks (28 to 30 days) after vaccination. Importantly, no live vaccines should be given to individuals on LNP023 at this early stage of development.

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4.5.3 Potential safety risks for rituximab

The known adverse events and potential safety risks for rituximab (the reference treatment) include: infusion reactions, the large majority of which occur in association with the first infusion and within 24 hours of infusion, severe mucocutaneous reactions, hepatitis B reactivation, sometimes resulting in fulminant hepatitis, hepatic failure and death, and progressive multifocal leukoencephalopathy resulting in death. For detailed information on these risks and other AEs, refer to the SmPC/local country label. It is recommended that rituximab infusion is discontinued for severe reactions and that medical treatment is provided for Grade 3 and Grade 4 infusion–related reactions. Rituximab should be discontinued in the event of severe mucocutaneous reactions, hepatitis B virus reactivation or progressive multifocal leukoencephalopathy.

4.5.4 Preclinical safety findings of undetermined relevance for LNP023

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4.5.4.1 COVID-19 related risks

The COVID-19 pandemic may pose a challenge to integrity of the trial, protection of subjects' rights, safety and wellbeing, as well as the safety of study staff. Therefore, risk mitigation strategies have been established and will be evaluated on an ongoing basis for the duration of the study, or until there is a consensus that the period of the SARS-CoV-2 outbreak has passed. During the pandemic situation, further measures according to recommendations and requirements from local health authorities may become necessary and will be followed within the context of this study as far as applicable in order to ensure full implementation of the principles of GCP with priority on the safety of the subjects and study staff and the integrity of the data collected.

4.5.4.2 Risk for study subjects and site staff

LNP023 is a small molecule that blocks complement factor B (FB) and thereby the complement alternative pathway, which is important for the defense against microbes. Patients with mutations of FB are generally healthy but have impaired resistance against bacterial infections and in particular encapsulated bacteria. Complement does not seem to be involved in the direct immune response against viruses and moreover the inhibition of the complement system may lessen the cytokine storm and improve respiratory outcomes in severe COVID-19 pneumonia.

Regarding Rituximab, immunosuppressive drugs are cited as risk factors for severe forms of COVID-19. However, rituximab may have the potential to lessen the cytokine storm and improve respiratory outcomes in severe COVID-19 pneumonia.

To reduce the risk of SARS-CoV-2 infections among subjects and site staff, sites in participating countries will follow measures and procedures as per national guidelines or regulatory requirements.

See Section 8.4.6 COVID-19 Contingency plan, for further details.

4.5.5 Overall risk-benefit

The complement system plays a major role in innate and adaptive immunity (Merle et al 2015a). The AP utilizes C3 fragments (C3b) to opsonize pathogens, hence targeting them for phagocytosis without the need for antibodies (Merle et al 2015b). Hyperactivity of the complement system, and in particular in its AP, seems to cause, or exacerbate, a large number of diseases. Thus, there is a potential benefit of blocking the AP for patients with complement-driven diseases. LNP023 is a potent and selective oral small molecule inhibitor of FB, which is a key component of the AP. The compound has first-in-class potential and is being developed in renal diseases: IgA nephropathy, C3 glomerulopathy and membranous nephropathy, as well as the blood disorder paroxysmal nocturnal hemoglobinuria.

Based on its mechanism of action, the main risk of treatment with LNP023 is infection. An intact complement system is particularly important for defense against encapsulated bacteria (e.g. *Neisseria meningitidis, Streptococcus pneumoniae,* and *Haemophilus influenzae*). Patients with factor B loss-of-function mutations are more susceptible to such infections (Slade et al 2013). The mitigation strategies are to vaccinate patients, and for patients and physicians to be extra vigilant for infection symptoms. Data suggest that the protective effect of vaccination is maintained after blockade of the AP but not after terminal pathway (e.g. C5) blockade (Konar and Granoff 2017).

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Overall, the data available to date support LNP023 treatment of diseases such as C3G, PNH, aHUS, IgAN and MN. The risk-benefit relationship for LNP023 remains positive.

Rituximab is not registered for use in idiopathic membranous nephropathy, however has been extensively investigated in the MENTOR and GEMRITUX studies (Fervenza et al 2015; Dahan et al 2017). Data from the MENTOR/GEMRITUX studies in MN do not suggest that the safety/tolerability profile of rituximab would differ from other rituximab indications. A summary of the outcomes and adverse effects of rituximab therapy are outlined above in Section 4.5.

4.5.5.1 COVID-19 risk-benefit

In the light of all measures implemented in this study to prevent and mitigate the COVID-19 pandemic related risks, the benefit/risk assessment of the conduct of this study is positive also during the COVID-19 pandemic situation in its current extent. The benefit/risk assessment will be continuously monitored during the conduct of this study and will be updated in accordance to changes of the COVID-19 pandemic situation and related authority regulations and recommendations.

4.5.6 Risk mitigation strategy

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There are CCI potential risks that have been identified namely 'infections,' Commercially Confidential Information The former is mitigated by vaccinations against encapsulated bacteria as described in Section 4.5.3.

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Patients will return to the clinic on a regular basis. During these visits safety, tolerability, efficacy and PK/PD data will be collected. Standard safety assessments will include vital signs, physical examinations, ECG, clinical laboratory evaluations (hematology, blood chemistry and urinalysis), and AEs as outlined in the Assessment schedule (Table 8-1 and Table 8-2). In addition to standard clinical laboratory assessments, subjects will be monitored regularly for

signs and symptoms of infections, Commercially Confidential Information will be informed to report any symptoms to the clinical staff to assure proper assessment and so that care can be administered in a timely manner.

For patients in the rituximab arm, sites will be asked to follow local guidelines for administration of the i.v. infusion, including the rate of administration, use of premedication, frequency of observation of vital signs and monitoring for evidence of infusion reactions.

Clinical laboratory evaluations and standard safety assessments will be performed per the Assessment Schedule (Table 8-1 and Table 8-2) to monitor for signs and symptoms of adverse events.

In agreement with the primary and secondary objectives, measurement of UPCR CCI , 24-h urine excretion of albumin and protein will be made, and changes in renal function will be assessed via serum creatinine and estimated glomerular filtration rate (eGFR, Chronic Kidney Disease - Improved Prediction Equations (CKD-EPI)).

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A priori defined stopping criteria and guidelines (Section 9.1.4) in addition to the clinical opinion of the investigator will be used to protect individual patient safety during the trial.

COVID-19 specific risk mitigation strategies (Section 8.4.6) were implemented in this study as part of the clinical study procedures. Finally, key safety data will be reviewed by the sponsor on an ongoing basis.

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Population

A total of approximately 52 male or female subjects are planned to be randomized into the study: approximately 24 on LNP023 200 mg, approximately 24 on rituximab Commercially Confidential Information . The investigator must ensure that all subjects being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the investigator, in order that the study population will be representative of all eligible subjects.

Subject selection is to be established by checking through all eligibility criteria at screening and baseline. A relevant record (e.g., checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from any entry criterion excludes a subject from enrollment into the study.

5.1 Inclusion criteria

Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Written informed consent must be obtained before any study assessment is performed.
2. Able to communicate well with the investigator, to understand and comply with the requirements of the study.
3. Female or male adult (≥18 years) subjects at screening visit with a diagnosis of idiopathic (primary) MN confirmed by renal biopsy within 36 months prior to screening. A renal biopsy may be taken at any time during the run-in period to confirm the diagnosis of MN and facilitate subject eligibility, if the most recent biopsy was performed greater than 36 months prior to the screening visit.
4. Anti-PLA2R antibody titer of ≥ 60 RU/mL at screening visit (based on the EuroImmun ELISA test). If the sites opt to use a local laboratory, with prior agreement with sponsor, an anti-PLA2R titer performed within 4 weeks prior to screening visit can be used.
5. ≤50% reduction in both anti-PLA2R level and 24h urine protein between first measurement at screening or run-in visit and baseline.
6. Urine protein ≥3.5 g/24h at run-in and baseline visits.
7. Estimated GFR (using the CKD-EPI formula) ≥30 mL/min per 1.73 m^2 at screening visit.
8. Commercially Confidential Information
9. Receiving stable dose at the maximum recommended dose according to local guidelines or maximum tolerated dose of ACEi and/or ARB and/or statins and/or diuretics. The dose of ACEi or ARB must be stable for at least 8 weeks prior to Day 1, defined as <25% dose change over this 8 week period.
10. Vaccination against *Neisseria meningitidis, Streptococcus pneumoniae* and *Haemophilus influenzae* (in accordance with local guidelines) at least 28 days prior to Day 1 and no longer than 5 years prior to Day 1.
11. Subject agrees to collect 24h urine sample at home and to bring it to the investigational site at specific visits.

5.2 Exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study.

1. Secondary causes of MN, e.g. systemic autoimmune diseases, solid or hematological malignancies, infections or chronic intake of drugs (e.g. gold salts, NSAIDs, penicillamines)
2. Diagnostic renal biopsy showing evidence of crescent formation in glomeruli, suggestive of an alternative or additional diagnosis to primary idiopathic MN.
3. Previous treatment with B-cell depleting or B-cell modifying agents such as, but not limited to rituximab, belimumab, daratumumab or bortezomib.
4. Previous treatment with immunosuppressive agents such as cyclophosphamide, chlorambucil, mycophenolate mofetil (or equivalent), cyclosporine, tacrolimus or azathioprine within 90 days prior to Day 1. Low dose systemic corticosteroid therapy is permitted, though the subject should have been on stable dose equivalent to ≤10 mg prednisolone for at least 90 days prior to Day 1
5. Commercially Confidential Information

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10. Presence or suspicion (based on judgment of the investigator) of any active infection within 30 days prior to Day 1, or history of severe recurrent bacterial infections
11. Pregnancy or nursing (lactation), where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human Chrorionic Gonadotropin (hCG) laboratory test
12. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective contraception during dosing and for 1 week after stopping of LNP023 or for 12 months after stopping rituximab. *Effective contraception methods include:*
    - Barrier methods of contraception: Condom or Occlusive cap.
    - Use of oral, injected or implanted hormonal methods of contraception, or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception, or placement of an intrauterine device (IUD) or intrauterine system (IUS). In case of use of oral contraception, you should have been stable on the same pill for a minimum of 3 months before taking the study treatment.
    - Total abstinence (When this is in line with your preferred and usual lifestyle. Periodic abstinence and withdrawal are not acceptable methods of contraception)
    - Female sterilization (surgical bilateral oophorectomy [with or without hysterectomy], total hysterectomy or tubal ligation, at least six weeks before taking study treatment. In case of oophorectomy alone, only when your reproductive status has been confirmed by follow up hormone level assessment)
    - Your sole partner is a vasectomized male who was sterilized at least 6 months prior to screening.

    In case of use of oral contraception, women should be stable on the same pill for a minimum of 3 months before taking study treatment.

If local regulations deviate from the contraception methods listed above and require more extensive measures to prevent pregnancy, local regulations apply and will be described in the ICF.

Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea at screening with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks prior to screening. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential

13. History of immunodeficiency diseases, including a positive HIV test result at screening visit
14. Commercially Confidential Information
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23. Known contraindications for the use of rituximab, including hypersensitivity to the active substance or to murine proteins, or to any of the excipients (sodium citrate, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid, water for injections).
Other contra-indications for the use of rituximab, including active, severe infection, patients in a severely immunocompromised state, severe heart failure (NYHA ClassIV) or severe, uncontrolled cardiac disease.

24. Evidence of TB infection (active or latent) determined by positive QuantiFERON test or positive purified protein derivative (PPD) test (≥5 mm induration) at screening visit or within 2 months prior to screening visit, according to national guidelines. Patients with a positive or indeterminate QFT test may participate in the study if a full tuberculosis work-up (according to local practice/guidelines) completed within 12 weeks prior to randomization, establishes conclusively that the patient has no evidence of active or latent tuberculosis. If presence of latent TB infection is established then treatment for TB as per national guidelines must have been initiated and completed prior to randomization. In the absence of national guidelines, the following has been demonstrated: TB has been treated adequately by antibiotics, cure can be demonstrated and risk factors resulting in TB exposure and contracting have been removed.
    - Subjects who in the opinion of the investigator and based upon an appropriate evaluation, have a risk of reactivation of TB that precludes the use of conventional immunosuppression

6 Treatment

6.1 Study treatment

Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing, and taking study treatment are outlined in the SOM.

6.1.1 Investigational and control drugs

The investigational drug LNP023 will be prepared by the sponsor as 25 mg and 100 mg capsules. Investigational drug will be supplied to the investigator as patient-specific kits.

All LNP023-treated subjects will be administered two capsules at morning and evening during treatment period. Refer to SOM for details on dispensing.

The investigational drug rituximab as concentrate for solution for infusion will be provided locally. Refer to the SOM for specific instructions on preparation.

Table 6-1 Investigational and control drug

Investigational/ Control Drug	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global) or locally provided
LNP023 25 mg	Capsules	Oral use	patient specific kits	Sponsor (global)
LNP023 100 mg	Capsules	Oral use	patient specific kits	Sponsor (global)
Rituximab 10 mg/mL*	Concentrate for solution for infusion	Intravenous use	Open label subject packs	Locally provided

* Concentration can vary based on country availabilities.

6.1.2 Additional study treatments

No other treatment beyond investigational drugs are included in this trial.

6.1.3 Treatment arms/group

This is an open-label study. Subjects will be assigned at Day 1, or up to 4 days before, if all the inclusion and exclusion criteria are verified, to one of the following treatment arms in a ratio of 1:1

- LNP023 Commercially Confidential Information
- Rituximab 1 g i.v. at Day 1 and Day 15

6.2 Other treatment(s)

Not applicable.

6.2.1 Concomitant therapy

The investigator must instruct the subject to notify the study site about any new medications he/she takes after being enrolled in the study.

Subjects must receive vaccinations against *N. meningitidis*, *S. pneumoniae* and *H. influenzae* at least 28 days prior to Day 1 independent of the treatment arm allocation (see Section 8.4.4 for more details).

Prophylactic antibiotics may be given at investigator's discretion in accordance with local practice for patients receiving immunosuppressive or complement pathway blocking therapies. Prophylactic antibiotic therapy may be given for tuberculosis as per local guidelines.

Subjects will remain on their supportive therapy, e.g. ACEi and/or ARB and or systemic corticosteroids, with or without diuretics, statins or antihypertensive therapy(ies) for the duration of the trial. To be commenced on randomized treatment, subjects must have been on stable therapy with an ACEi and/or ARB, defined as <25% dose change over at least 8 weeks at the maximally tolerated dose (KDIGO 2012) and, if used as part of local standard of care, systemic corticosteroids at a stable dose that does not exceed the equivalent of 10 mg prednisolone daily over at least 90 days prior to Day 1.

Subjects in the rituximab arm should receive pre-medication consisting of an anti-pyretic and an antihistamine (e.g. paracetamol and diphenhydramine) before each dose as per local standards. Where a single dose of glucocorticoid (e.g. methylprednisolone or hydrocortisone) is used in addition to these measures as part of local standard of care, then this is permitted.

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded on the appropriate Case Report Forms.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the sponsor medical monitor before randomizing a subject or allowing a new medication to be started. If the subject is already enrolled, contact sponsor to determine if the subject should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

LNP023

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Rituximab

The co-administration of rituximab did not have any effect on the pharmacokinetics of fludarabine or cyclophosphamide and in addition there was no apparent effect of fludarabine and cyclophosphamide on the pharmacokinetics of rituximab. Co-administration of methotrexate had no impact on rituximab pharmacokinetics (Rituximab SmPc 2019).

6.2.2 Prohibited medication

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The investigator should consult with the Novartis medical expert prior to treating a patient with this type of co-medication.

Use of the treatments displayed in the tables below is NOT allowed.

Table 6-2 Prohibited medication for LNP023 arm

Medication	Prohibition period	Action taken
Live Vaccination	From 28 days prior to dosing until the end of randomized treatment period, unless immunosuppressive therapy commenced during safety follow-up period	Discontinue study treatment during treatment period. Ongoing study visits to collect outcome data.
Immunosuppressive agents such as but not limited to cyclophosphamide, MMF or mycophenolate sodium, cyclosporine, tacrolimus, sirolimus, systemic corticosteroids at a dose greater than 10mg/day prednisolone equivalent	90 Days prior to dosing until end of randomized treatment period.	Discontinuation of study treatment to be discussed and agreed on a case by case basis. Ongoing study visits to collect outcome data where study treatment is discontinued.
Biological agents such as, rituximab, infliximab, canakinumab, etc.	At any point prior to randomization or during the randomized treatment period	Discontinue study treatment during treatment period.Ongoing study visits to collect outcome data.

Table 6-3 Prohibited medication for rituximab arm

Medication	Prohibition period	Action taken
Live Vaccination	From 28 days prior to dosing until the end of randomized treatment period, unless immunosuppressive therapy commenced during safety follow-up period	Discontinue study treatment during treatment period. Ongoing study visits to collect outcome data.
Immunosuppressive agents such as but not limited to cyclophosphamide, MMF or mycophenolate sodium, cyclosporine, tacrolimus, sirolimus, systemic corticosteroids at a dose greater than 10mg/day prednisolone equivalent	90 prior to dosing and until end of randomized treatment period, except in case of pre-medication for infusion.	Discontinuation of study treatment to be discussed and agreed on a case by case basis. Ongoing study visits to collect outcome data where study treatment is discontinued.
Biological agents such as infliximab, canakinumab, etc.	At any point prior to randomization. Biological agents other than rituximab study drug should not be administered during the randomized treatment period	Discontinue study treatment during treatment period. Ongoing study visits to collect outcome data.

6.2.3 Restriction for study subjects

Subjects will be required to adhere to the measures and procedures outlined by the study site, to prevent SARS-CoV-2 infections among trial participants and clinical site staff.

6.2.3.1 Dietary restrictions and smoking

There are no specific dietary or smoking restrictions.

6.2.3.2 Other restrictions

Not applicable.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

The subject number assigned to a subject at screening visit remains the unique identifier for the subject throughout the study. For information on subject numbering, please see ‘Subject numbering’ section in the Site Operations Manual.

6.3.2 Treatment assignment, randomization

Upon signing the informed consent form by the subject, the investigator or his/her staff will contact the IRT and provide the requested identifying information to register a subject into the IRT.

A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

Randomization will occur on Day 1 or up to 4 days before, after eligibility is confirmed.

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The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

Follow the details outlined in the Site Operations Manual regarding the process and timing of treatment assignment and randomization of subjects.

6.4 Treatment blinding

This is an open-label study, so blinding is not applicable.

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6.5 Dose escalation and dose modification

Commercially Confidential Information

Investigational or other study treatment dose adjustments are not permitted for LNP023 and rituximab.

6.6 Additional treatment guidance

Rituximab-treated subjects may receive premedication with antihistamines, paracetamol / acetaminophen and/or corticosteroids in accordance with local practice for the prevention of infusion reaction.

For subjects treated with LNP023, there is no need for additional treatments.

6.6.1 Treatment compliance

LNP023

The investigator must promote medication compliance by instructing the subject to take the study treatment (LNP023) exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance with LNP023 will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the subject in a diary. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log. Subjects with poor treatment compliance may be withdrawn from the study at the sponsor discretion.

Pharmacokinetic parameters (measures of treatment exposure) will only be determined in subjects treated with LNP023, as detailed in pharmacokinetics section (Section 8.5.2).

Rituximab

Compliance for the rituximab treatment regimen is ensured by treatment administration at study site as per Table 8-2.

6.6.2 Recommended treatment of adverse events

At present, there is insufficient information to provide specific recommendations regarding treatment of AEs for LNP023 arm. There is no treatment that can reverse the activity of LNP023. LNP023 is a small molecule CCI . Potential AEs should therefore be treated symptomatically at the discretion of the investigator. Medication used to treat AEs must be recorded on the concomitant medications/significant non-drug therapies CRF.

Rituximab-related AEs should be treated in accordance with local guidelines. Patients who develop infusion reactions should be monitored closely. The rituximab infusion should be discontinued and medical treatment with corticosteroids, antihistamine and paracetamol should be administered in accordance with local guidelines for severe reactions. Rituximab therapy should be discontinued in the event of severe mucocutaneous reactions, hepatitis B reactivation, neurological complications or other serious adverse events deemed by the investigator to be treatment related.

Where response to treatment is deemed inadequate the investigator may, at their discretion, withdraw the subject from the study and commence local standard of care. Subjects should continue with the scheduled study visits to allow collection of outcome and adverse event data.

6.6.3 Emergency breaking of assigned treatment code

The study is open label between LNP023 and rituximab treatment. As soon as the protocol amendment v01 is implemented in the country, there would be no more blinding between the former LNP023 regimens, so this section will no longer be applicable.

6.7 Preparation and dispensation

Each study site will be supplied with LNP023 in packaging as described under the investigational and control drugs section (Section 6.1.1). Rituximab will be supplied locally.

LNP023

LNP023 will be administered to the subject via the following route of administration: oral. Commercially Confidential Information

Rituximab

Rituximab will be administered at the study site via the following route of administration: i.v.

Site staff will prepare and administer 1 g rituximab doses on Day 1 and Day 15.

See the Site Operations Manual and rituximab SmPC/local country label for further details on preparation, handling, and administration.

Subjects in the rituximab arm should receive pre-medication consisting of an anti-pyretic and an antihistamine (e.g. paracetamol and diphenhydramine) before each dose as per local standards. Where a single dose of glucocorticoid (e.g. methylprednisolone or hydrocortisone) is used in addition to these measures as part of local standard of care, then this is permitted.

Public Health emergency Guidance

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of IMP directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the participant's home remains under the accountability of the investigator. Each shipment/provisioning will be agreed with Novartis. In this case, regular phone calls or virtual contacts (every 2 weeks or as frequent as needed) will occur between the site and the participant for instructional purposes, safety monitoring, drug accountability, investigation of any adverse events, ensuring participants

continue to benefit from treatment and discussion of the participant´s health status until the participants can resume visits at the study site.

6.7.1 Rescue medication

Not applicable.

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation) IRB/IEC-approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB) for LNP023 and the SmPC/local country label of rituximab. Some common safety risks with rituximab are listed in Section 4.5.3. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

Women of childbearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study, they must adhere to the contraception requirements.

The study includes an optional DNA component which requires a separate signature if the subject agrees to participate. It is required as part of this protocol that the investigator presents this option to the subjects, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in this optional assessment (DNA) will in no way affect the subject’s ability to participate in the main research study.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities, i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, the investigator

may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Heath Authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

A copy of the approved version of all consent forms must be provided to sponsor after IRB/IEC approval.

Refer to the Site Operations Manual for a complete list of ICFs included in this study.

8 Visit schedule and assessments

Assessment Schedule (Table 8-1 and Table 8-2) lists all of the assessments and when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Subjects should be seen for all visits/assessments as outlined in the Assessment Schedule (Table 8-1 and Table 8-2) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care and of samples/endpoints/COA collection may be implemented by the investigator as the situation dictates. If allowed by local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff / home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

If visits by site staff to a participant's home are not feasible, the collection of samples and/or endpoints may be modified by Novartis and will be communicated to the investigator.

Table 8-1 Assessment Schedule, LNP023 arm

Period	Screening				Treatment														
Visit Name	Screening	Run-in		Baseline[15]	Day 1		Day 15	Day 29							Day 57	Day 85	Day 113			
Days	-83 to -76	-82 to -75	-40 to -30	-15 to -10	1		15 ±2	29 ±2							57 ±3	85 ±3	113 ±3			
Weeks of treatment	-12 to -11	-12 to -11	-6 to -5	-3 to -2	0		2	4							8	12	16			
Time (post-dose)	-	-	-	-	Pre-dose[1]	1 h	Pre-dose[1]	Pre-dose[1]	0.25 h	0.5 h	1 h	2 h	4 h	6 h	Pre-dose[1]	Pre-dose[1]	Pre-dose[1]	0.25 h	0.5 h	1h
Informed consent[2]	X																			
CCI	X																			
Inclusion / Exclusion criteria	X			X																
Vaccination		X	X[4]																	
Renal biopsy[5]		X																		
Medical history/current medical conditions	X																			
Pregnancy and assessments of fertility[6]	S			S				S							S	S	S			
Hepatitis and HIV Screen	S																			
Demography	X																			
Pulse rate	X			X	X	X	X	X				X			X	X	X			
Blood Pressure	X			X	X	X	X	X				X			X	X	X			
Body Temperature	X			X	X		X	X							X	X	X			
Physical Examination	S			S			S										S			

Period	**Screening**				**Treatment**															
Visit Name	**Screening**	**Run-in**		**Baseline[15]**	**Day 1**		**Day 15**	**Day 29**						**Day 57**	**Day 85**	**Day 113**				
Days	**-83 to -76**	**-82 to -75**	**-40 to -30**	**-15 to -10**	**1**		**15 ±2**	**29 ±2**						**57 ±3**	**85 ±3**	**113 ±3**				
Weeks of treatment	**-12 to -11**	**-12 to -11**	**-6 to -5**	**-3 to -2**	**0**		**2**	**4**						**8**	**12**	**16**				
Time (post-dose)	**-**	**-**	**-**	**-**	**Pre-dose[1]**	**1 h**	**Pre-dose[1]**	**Pre-dose[1]**	**0.25 h**	**0.5 h**	**1 h**	**2 h**	**4 h**	**6 h**	**Pre-dose[1]**	**Pre-dose[1]**	**Pre-dose[1]**	**0.25 h**	**0.5 h**	**1h**
Body Height	X																			
Body Weight	X			X	X		X	X							X	X	X			
Tuberculosis status	X																			
Hematology	X			X	X		X	X							X	X	X			
Urinalysis	X			X	X[7]		X[7]	X[7]							X[7]	X[7]	X[7]			
Clinical Chemistry	X			X	X		X	X							X	X	X			
CCI	X			X	X		X	X							X	X	X			
Electrocardiogram (ECG)	X			X	X	X	X	X				X			X	X	X			
24h urine collection[8]		X		X													X			
First morning void		X[9]		X[9]			X	X							X	X	X[9]			
CCI				X				X[7]									X[7]			
Estimated glomerular filtration rate	X			X	X		X	X							X	X	X			
CCI				X			X	X							X	X	X			

Period	**Screening**				**Treatment**															
Visit Name	**Screening**	**Run-in**		**Baseline[15]**	**Day 1**		**Day 15**	**Day 29**							**Day 57**	**Day 85**	**Day 113**			
Days	**-83 to -76**	**-82 to -75**	**-40 to -30**	**-15 to -10**	**1**		**15 ±2**	**29 ±2**							**57 ±3**	**85 ±3**	**113 ±3**			
Weeks of treatment	**-12 to -11**	**-12 to -11**	**-6 to -5**	**-3 to -2**	**0**		**2**	**4**							**8**	**12**	**16**			
Time (post-dose)	**-**	**-**	**-**	**-**	**Pre-dose[1]**	**1 h**	**Pre-dose[1]**	**Pre-dose[1]**	**0.25 h**	**0.5 h**	**1 h**	**2 h**	**4 h**	**6 h**	**Pre-dose[1]**	**Pre-dose[1]**	**Pre-dose[1]**	**0.25 h**	**0.5 h**	**1h**
Anti-PLA2R[11]	X			X				X												
PK blood collection[12]							X	X	X	X	X	X	X	X	X		X	X	X	X
CCI				X			X	X						X	X		X			
Complement biomarkers in plasma				X			X	X						X	X		X			
CCI					X															
Randomization					X[13]															
Study drug administration (LNP023)[14]					b.i.d.															
CCI					X		X							X	X	X				
Patient diary					X															
CCI				X			X	X							X		X			
CCI				X			X	X							X		X			

Period	**Screening**				**Treatment**															
Visit Name	**Screening**	**Run-in**		**Baseline[15]**	**Day 1**		**Day 15**	**Day 29**							**Day 57**	**Day 85**	**Day 113**			
Days	**-83 to -76**	**-82 to -75**	**-40 to -30**	**-15 to -10**	**1**		**15 ±2**	**29 ±2**							**57 ±3**	**85 ±3**	**113 ±3**			
Weeks of treatment	**-12 to -11**	**-12 to -11**	**-6 to -5**	**-3 to -2**	**0**		**2**	**4**							**8**	**12**	**16**			
Time (post-dose)	**-**	**-**	**-**	**-**	**Pre-dose[1]**	**1 h**	**Pre-dose[1]**	**Pre-dose[1]**	**0.25 h**	**0.5 h**	**1 h**	**2 h**	**4 h**	**6 h**	**Pre-dose[1]**	**Pre-dose[1]**	**Pre-dose[1]**	**0.25 h**	**0.5 h**	**1h**
Concomitant medications	X																			
Safety Follow up Call																				
Adverse Events	X																			
Serious Adverse Events	X																			
Study completion information																				

Period	Treatment					Post-Treatment Follow-Up		
Visit Name	Day 113			Day 141	Day 169	Safety follow-up call	Day 266	EOS
Days	113 ±3			141 ±3	169 ±3	199 ±3	266 ±3	378 ±5
Weeks of treatment	16			20	24	28	37	53
Time (post-dose)	2h	4h	6h	Pre-dose[1]	Pre-dose[1]	-	-	-
Informed consent[2]								
CCI								
Inclusion / Exclusion criteria								
Vaccination								
Renal biopsy[5]								
Medical history/current medical conditions								
Pregnancy and assessments of fertility[6]				S	S		S	S
Hepatitis and HIV Screen								
Demography								
Pulse rate	X			X	X		X	X
Blood Pressure	X			X	X		X	X
Body Temperature				X	X		X	X
Physical Examination					S		S	S
Body Height								
Body Weight				X	X		X	X
Tuberculosis status								
Hematology				X	X		X	X
Urinalysis				X[7]	X[7]		X	X
Clinical Chemistry				X	X		X	X
CCI				X	X		X	X
Electrocardiogram (ECG)	X			X	X			X

Period	**Treatment**					**Post-Treatment Follow-Up**		
Visit Name	**Day 113**			**Day 141**	**Day 169**	**Safety follow-up call**	**Day 266**	**EOS**
Days	**113 ±3**			**141 ±3**	**169 ±3**	**199 ±3**	**266 ±3**	**378 ±5**
Weeks of treatment	**16**			**20**	**24**	**28**	**37**	**53**
Time (post-dose)	**2h**	**4h**	**6h**	**Pre-dose[1]**	**Pre-dose[1]**	**-**	**-**	**-**
24h urine collection[8]					X			
First morning void				X	X[9]		X	X
CCI					X[7]		X	
Estimated glomerular filtration rate				X	X		X	X
CCI				X	X		X	X
Anti-PLA2R[11]					X		X	
PK blood collection[12]	X	X	X		X			
CCI			X		X		X	
Complement biomarkers in plasma			X		X		X	
CCI								
Randomization								
Study drug administration (LNP023)[14]	b.i.d.							
Study drug dispensing			X	X				
Patient diary	X							
CCI					X			
CCI					X			
Concomitant medications	X							

Period	Treatment					Post-Treatment Follow-Up		
Visit Name	Day 113			Day 141	Day 169	Safety follow-up call	Day 266	EOS
Days	113 ±3			141 ±3	169 ±3	199 ±3	266 ±3	378 ±5
Weeks of treatment	16			20	24	28	37	53
Time (post-dose)	2h	4h	6h	Pre-dose[1]	Pre-dose[1]	-	-	-
Safety Follow up Call						S		
Adverse Events	X							
Serious Adverse Events	X							
Study completion information								X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] All timing is related to the first administration of investigational drug
[2] Written informed consent to be obtained prior to any study-related procedure
[3] Commercially Confidential Information

[4] If needed a second dose of vaccines can be administered at this visit.
[5] If last biopsy available is older than 36 months at screening visit
[6] Serum pregnancy at screening and Day 169. Urine pregnancy test for the remaining visits.
[7] If patient cannot urinate at this timepoint, sample can be collected post-dose, and time should be recorded.
[8] 24h urine collection starts in the morning of the day before, after collection of first morning void in a separate jug, and ends in the morning of the day of visit.
[9] Collect First morning void and then start 24h urine collection
[10] At selected sites
[11] Collected for all patients at screening and baseline visits. An existing anti-PLA2R value of less than 4 weeks prior to the screening visit may be acceptable after agreement with the sponsor
[12] Pre-dose PK sample should be collected within a window of 10 minutes before the subject takes the dose.
[13] After eligibility is confirmed and up to 4 days before Day 1
[14] Commercially Confidential Information
[15] Baseline period can be extended in case of delays in receiving anti-PLA2R results

Table 8-2 Assessment Schedule, Rituximab arm

Period	Screening				Treatment								Post-Treatment Follow-Up		
Visit Name	**Screening**	**Run-in**		**Baseline[13]**	**Day 1**	**Day 15**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169**	**Safety follow-up call**	**Day 266**	**EOS**
Days	**-83 to -76**	**-82 to -75**	**-40 to -30**	**-15 to -10**	**1**	**15 ±2**	**29 ±2**	**57 ±3**	**85 ±3**	**113 ±3**	**141 ±3**	**169 ±3**	**199 ±3**	**266 ±3**	**378 ±5**
Weeks of treatment	**-12 to -11**	**-12 to -11**	**-6 to -5**	**-3 to -2**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**37**	**53**
Time (post-dose)	**-**	**-**	**-**	**-**	**Pre-dose[1]**	**Pre-dose[1]**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Informed consent[2]	X														
CCI	X														
Inclusion / Exclusion criteria	X			X											
Vaccination		X	X[4]												
Renal biopsy[5]		X													
Medical history/current medical conditions	X														
Pregnancy and assessments of fertility[6]	S			S			S	S	S	S	S	S		S	S
Hepatitis and HIV Screen	S														
Demography	X														
Pulse rate	X			X	X	X	X	X	X	X	X	X		X	X
Blood Pressure	X			X	X	X	X	X	X	X	X	X		X	X
Body Temperature	X			X	X	X	X	X	X	X	X	X		X	X
Physical Examination	S			S		S				S		S		S	S
Body Height	X														
Body Weight	X			X	X	X	X	X	X	X	X	X		X	X

Period	Screening				Treatment								Post-Treatment Follow-Up		
Visit Name	**Screening**	**Run-in**		**Baseline**[13]	**Day 1**	**Day 15**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169**	**Safety follow-up call**	**Day 266**	**EOS**
Days	**-83 to -76**	**-82 to -75**	**-40 to -30**	**-15 to -10**	**1**	**15 ±2**	**29 ±2**	**57 ±3**	**85 ±3**	**113 ±3**	**141 ±3**	**169 ±3**	**199 ±3**	**266 ±3**	**378 ±5**
Weeks of treatment	**-12 to -11**	**-12 to -11**	**-6 to -5**	**-3 to -2**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**37**	**53**
Time (post-dose)	**-**	**-**	**-**	**-**	**Pre-dose**[1]	**Pre-dose**[1]	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Tuberculosis status	X														
Clinical Chemistry	X			X	X	X	X	X	X	X	X	X		X	X
CCI	X			X	X	X	X	X	X	X	X	X		X	X
Hematology	X			X	X	X	X	X	X	X	X	X		X	X
Urinalysis	X			X	X[7]	X[7]	X	X	X	X	X	X		X	X
Electrocardiogram (ECG)	X			X	X	X	X	X	X	X	X	X			
24h urine collection[8]		X		X						X		X			
First morning void		X[9]		X[9]		X	X	X	X	X[9]	X	X[9]		X	X
CCI				X			X			X		X		X	
Estimated glomerular filtration rate	X			X	X	X	X	X	X	X	X	X		X	X
CCI				X		X	X	X	X	X	X	X		X	X
Anti-PLA2R[11]	X			X			X					X		X	
Complement biomarkers in plasma				X		X	X	X		X		X		X	

Period	Screening				Treatment								Post-Treatment Follow-Up		
Visit Name	**Screening**	**Run-in**		**Baseline[13]**	**Day 1**	**Day 15**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169**	**Safety follow-up call**	**Day 266**	**EOS**
Days	**-83 to -76**	**-82 to -75**	**-40 to -30**	**-15 to -10**	**1**	**15 ±2**	**29 ±2**	**57 ±3**	**85 ±3**	**113 ±3**	**141 ±3**	**169 ±3**	**199 ±3**	**266 ±3**	**378 ±5**
Weeks of treatment	**-12 to -11**	**-12 to -11**	**-6 to -5**	**-3 to -2**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**37**	**53**
Time (post-dose)	**-**	**-**	**-**	**-**	**Pre-dose[1]**	**Pre-dose[1]**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
CCI				X		X	X	X		X		X		X	
CCI					X		X					X			
CCI					X										
Randomization					X[12]										
Study drug administration (rituximab)					X	X									
Patient diary					X										
CCI				X		X	X	X		X		X			
CCI				X		X	X	X		X		X			
Concomitant medications	X														
Safety Follow up Call													S		

Period	Screening				Treatment								Post-Treatment Follow-Up		
Visit Name	**Screening**	**Run-in**		**Baseline[13]**	**Day 1**	**Day 15**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 169**	**Safety follow-up call**	**Day 266**	**EOS**
Days	**-83 to -76**	**-82 to -75**	**-40 to -30**	**-15 to -10**	**1**	**15 ±2**	**29 ±2**	**57 ±3**	**85 ±3**	**113 ±3**	**141 ±3**	**169 ±3**	**199 ±3**	**266 ±3**	**378 ±5**
Weeks of treatment	**-12 to -11**	**-12 to -11**	**-6 to -5**	**-3 to -2**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**37**	**53**
Time (post-dose)	**-**	**-**	**-**	**-**	**Pre-dose[1]**	**Pre-dose[1]**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Adverse Events	X														
Serious Adverse Events	X														
Study completion information															X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] All timing is related to the first administration of investigational drug
[2] Written informed consent to be obtained prior to any study-related procedure
[3] Commercially Confidential Information

[4] If needed a second dose of vaccines can be administered at this visit.
[5] If last biopsy available is older than 36 months at Screening
[6] Serum pregnancy at Screening and Day 378. Urine pregnancy test for the remaining visits.
[7] If patient cannot urinate at this timepoint, sample can be collected post-dose, and time should be recorded.
[8] 24h urine collection starts in the morning of the day before, after collection of first morning void in a separate jug, and ends in the morning of the day of visit.
[9] Collect First morning void and then start 24h urine collection
[10] At selected sites
[11] Collected for all patients at screening and baseline visits. An existing anti-PLA2R value of less than 4 weeks prior to the screening visit may be acceptable after agreement with the sponsor
[12] After eligibility is confirmed and up to 4 days before Day 1
[13] Baseline period can be extended in case of delays in receiving anti-PLA2R results

8.1 Screening

In the case where a safety laboratory assessment at screening, run-in and/or baseline visit is outside of the range specified in the exclusion criteria, the assessment may be repeated once prior to randomization. Similarly, the anti-PLA2R antibodies assessment may be repeated once at screening and/or baseline after agreement from the sponsor. If the repeat value remains outside of the specified ranges, the subject must be excluded from the study.

It is permissible to re-screen a subject only once if s/he fails the initial screening; however, each case must be discussed and agreed with the sponsor on a case-by-case basis.

8.1.1 Information to be collected on screening failures

Refer to SOM for details on information to be collected for Screening failures.

8.1.2 Hepatitis screen, HIV screen

All subjects will be screened for HIV, Hepatitis B and C. See the Site Operations Manual for details.

8.1.3 Renal biopsy for screening evaluation

The diagnosis of MN must be based on a renal biopsy not older than 36months prior to screening visit. Where biopsies were performed ≥36 months prior to screening visit, subjects will be asked to perform a new renal biopsy during run-in to allow eligibility for the study. The biopsy should be performed after initial confirmation of eligibility at screening and run-in visits. Evaluation of the biopsy should be performed locally at site and reported in Source Data.

8.1.4 Anti-PLA2R

Anti-PLA2R antibodies titers will be measured using the quantitative ELISA assay from Euroimmun. Central laboratory testing will be available to all sites. However, after agreement with the sponsor, sites may decide to use an appropriately qualified local laboratory at the screening and baseline visits, on top of the central laboratory testing. All post baseline measurements shall be done using the central laboratory testing.

Sites should consistently use the local laboratory for screening and randomization visits for all their patients if agreed so with sponsor.

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The local laboratory anti-PLA2R titer prevails for screening and randomization purposes.Refer to SOM for more details.

8.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects. Relevant medical history/current medical conditions data will also be collected until signature of informed consent.

Subject demographics will include age, sex, race, ethnicity, height, weight and BMI. Other baseline disease characteristics include relevant medical history, current medical conditions, results of laboratory screens, and any other relevant information. Information on the duration of time before screening that the subject has been taking an ACEi/ARB/systemic corticosterid, and whether ACEi/ARB/systemic corticosteroid has been stable will also be collected.

Details are outlined in the Site Operations Manual.

Investigators have the discretion to record abnormal test findings on the medical history CRF, if in their judgment, the test abnormality occurred prior to the informed consent signature.

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

8.3 Efficacy

Pharmacodynamic samples will be collected at the timepoints defined in the Assessment Schedule (Table 8-1 and Table 8-2). Follow instructions outlined in the Site Operations Manual regarding sample collection, numbering, processing, and shipment.

8.3.1 Appropriateness of efficacy assessments

Primary endpoint

Reduction in proteinuria from baseline at week 24. This endpoint was chosen since the urinary protein level is known to correlate well to kidney function/inflammation, is a parameter closely related to disease progression and is expected to provide a sensitive and objective means to measure drug effect in comparison to baseline. Proteinuria will be assessed by collecting urine for 24 hours and measuring the protein to creatinine concentration ratio (UPCR). The total duration of the treatment period (6 months) is considered sufficient to observe relevant treatment effect on the selected primary endpoint based upon the published literature (Fervenza et al 2015; Dahan et al 2017) and guidelines (KDIGO 2012).

Secondary endpoints

Safety and tolerability of different doses of LNP023: this will allow the relative safety and tolerability of different LNP doses / exposure to be assessed. This, in combination with information generated in other studies of LNP023 (IgA nephropathy, C3G) will be used to inform dosing for future potential studies.

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Assessment of effect of LNP023 compared with rituximab on proteinuria remission and renal function: this will facilitate comparison of efficacy and safety with an agent which, whilst not currently registered for the treatment of membranous nephropathy, is currently in widespread use in this disorder.

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8.3.2 First morning void

First morning void urine sample for monitoring and other safety urine parameters will be collected 11 times by subject at home: 1 time at run-in, 1 time for baseline, 7 times during the treatment period and 2 times during safety follow-up.

When subject is asked to collect first morning void and 24h urine for the same visit, the first morning void will be collected in the morning of the day before the visit and kept in the fridge. Then the 24h urine collection will start just after the bladder is empty.

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8.3.3 24h urine collection

24h urine will be collected 4 times by the subject at home starting on the morning of the day prior study visit and brought to site the day of the visit: 1 time at run-in, 1 time for baseline, 1 time between Day 112 and Day 113, and 1 time between Day 168 and Day 169.

24h urine collection will start only after subject have completed the first morning void collection in a separate jug, and can be completed at site, if the 24h urine collection end coincide with site visit timing. Subjects will receive instructions on how to perform 24h urine collection at home and will record the start and end time of 24h urine collection on this document.

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8.3.4 Complement biomarkers in plasma (LNP023 arms)

Soluble complement biomarkers in circulation will be evaluated as potential pharmacodynamics and mode-of-action markers. They may include, but are not be limited to:

- Circulating fragment of factor B (Bb)
- sC5b-9

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8.4 Safety

Safety assessments are specified below with the Assessment Schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section (Section 10.1.1).

The methods, assessment, specification, and recording for each assessment will be detailed in the SOM.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (as determined after discussion with Novartis) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

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If participants cannot visit the site for protocol specified safety lab assessments, an alternative lab (local) collection site may be used.

Table 8-3 Assessments and Specifications

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs include BP and pulse measurements. After the subject has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured
Body temperature	Body temperature should be measured as per local practice – the same method to be used consistently for all patients at each site.

The methods for each assessment and data recording details are specified in the SOM.

8.4.1 Laboratory evaluations

All abnormal lab results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met. For those lab adverse events, repeated evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant.

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, MCH, MCHC, MCV, Platelets, Red blood cells, White blood cells, RBC Morphology, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Reticulocytes).
Chemistry	Albumin, Alkaline phosphatase, ALT , AST , Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL, HDL, Total Protein, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (non-fasting).
Urinalysis	Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells) Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen)

8.4.2 Electrocardiogram (ECG)

Full details of all procedures relating to the ECG collection and reporting are contained in the SOM.

All ECGs are done as 12-lead triplicate ECGs. All ECGs evaluations will be done by the investigators.

PR interval, QRS duration, heart rate, RR interval, QT interval, QTc.

The Fridericia QT correction formula (QTcF) must be used for clinical decisions.

As applicable, QTcF and QTcB may be calculated in-house. Unless auto-calculated by the ECG machine, the investigator must calculate QTcF at the screening and/or baseline visit(s) (as applicable) to assess eligibility. See the Site Operations Manual for additional details.

Clinically significant abnormalities must be reported as adverse events.

8.4.3 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

Assessments of Fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female subject regardless of reported reproductive/menopausal status at screening/baseline.

8.4.4 Vaccination

Subjects must receive vaccinations against *N. meningitidis*, *S. pneumoniae* and *H. influenzae* at least 28 days prior to Day 1 independent of the treatment arm allocation. If prior vaccination cannot be confirmed e.g. documented in subject's medical notes, subjects enrolling should be vaccinated against *N. meningitidis*, *S. pneumoniae* and *H. influenzae*. To ensure full protection, the vaccines against *N. meningitidis* should cover the most common serotypes. This can be done with for example MenveoTM covering A, C, W135 and Y in combination with BexseroTM against serotype B. In the US the serotypes C, B and Y accounts for 35%, 32% and 26% respectively, while serotype B is responsible for 2/3 of the cases in Europe (Sridhar et al 2015). Vaccination against *S. pneumoniae* can be done using for example Pneumovax™ (against 23 serotypes). Against *H. influenzae* vaccines such as Act-HIB^{TM} could be used. For all vaccinations, local recommendations and guidelines must be followed. All vaccine doses should be administered at least 28 days prior to first dosing. Continuous close monitoring of subjects for early symptoms and signs of infection is required in order to evaluate subjects immediately if an infection is suspected. Importantly, no live vaccines should be given to individuals on any treatment arm.

In case of previous vaccinations more than 5 years before Day 1, a booster dose should be administered according to local guidelines.

8.4.5 Tuberculosis status

Determination of TB status will be required before administration of study treatment and should be performed as defined by local guidelines.

Any significant findings will be recorded in the "Relevant medical history/Current medical conditions" section of the eCRF.

The quantiferon test for TB status will be analyzed by the central laboratory. Details on the collection, processing and shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual.

8.4.6 COVID-19 contingency plan

The sponsor recommends that subjects in the study are screened for symptomatic or asymptomatic carriage of SARS-CoV-2 at any time during the entire study duration as deemed necessary by the investigator taking in consideration the study site specific procedures and/or local and national regulatory requirements or guidelines.

Moreover, as part of the clinical study procedures, participants will be closely monitored for signs and symptoms of COVID-19 during the entire study duration.

Any subject that, in the opinion of the investigator, presents COVID-19-related symptoms and/or has a positive SARS-CoV-2 viral test, will be assessed on a case by case basis by the investigator (after consultation with Novartis, as applicable) to determine if the enrollment or further participation in the study is impacted.

For affected subjects randomized on the test treatment (LNP023) that are within the first 20 weeks of treatment period, the investigator may decide, if applicable, to pause the dosing of affected subject with study treatment for a period of maximum 3 weeks. If, however, the affected subject is within the last 4 weeks of the study treatment period and the investigator decides that the dosing with the study drug must be interrupted, the treatment for the affected subject will be then fully discontinued. Where possible, for paused or discontinued subjects, the upcoming assessments should be performed as per the assessment schedule.

In the case the investigator decides that the subject will be excluded from further participation in the study an EOS visit should be scheduled where possible. The affected subject will receive follow-up medical attention as per study site-specific procedures.

SARS-CoV-2 testing should always be performed as per national regulatory requirements or guidelines in participating countries.

8.5 Additional assessments

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8.5.2 Pharmacokinetics

PK samples will be collected at the visits defined in the assessment schedule for the LNP023 arm. Follow instructions outlined in the central laboratory manual regarding sample collection, numbering, processing, and shipment. See the potential use of residual samples for more information.

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The following pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental method(s): Cmax, Tmax, AUC, T1/2, from the plasma concentration-time data and the renal clearance (Clr) of LNP023 will be calculated from the amount excreted over 24h.

The linear trapezoidal rule will be used for AUC calculation. Regression analysis of the terminal plasma elimination phase for the determination of $T_{1/2}$ will include at least 3 data points after C_{max}. If the adjusted R^2 value of the regression analysis of the terminal phase will be less than 0.75, no values will be reported for $T_{1/2}$, AUC_{inf} and CL/F.

8.5.3 Biomarkers

Biomarkers studied may include, but are not limited to the following list:

- Biomarkers of the complement pathway activity / pharmacodynamic biomarkers:
  - Both arms: plasma levels of Complement fragment Bb of Factor B (Bb), sC5b-9 and Factor B; Commercially Confidential Information

Biomarkers relevant to secondary objectives (Bb and sC5b-9 in plasma) will be assessed at all sites involved in the study.

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Sample(s) will be collected at the time point(s) defined in the Assessment Schedules (Table 8-1 and Table 8-2).

Follow instructions for sample collection, numbering, processing, and shipment provided in the laboratory manual.

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8.5.4 Patient diaries

All patients will be handed with an adverse event diary to record any adverse event that occurs between study visits.

Patients that are assigned to LNP023 arm will receive a medication diary where they have to record the intake of study medication daily.

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatments for a patient occurs when study treatment is stopped earlier than the protocol planned duration. Discontinuation of study treatment can be decided by either the patient or the investigator. If discontinuation of study treatment occurs, the investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the Dosage Administration CRF.

Patients who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent. Where possible, they should perform the assessments as per assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the patient/pre-designated contact as specified. This contact should preferably be done according to the study visit schedule.

Test treatment (LNP023) or reference treatment (rituximab) must be discontinued under the following circumstances:

- Patient decision - Patients may choose to discontinue study treatment for any reason at any time.
- The investigator believes that continuation would negatively impact the safety of the patient or the risk/benefit ratio of trial participation.
- Any protocol deviation that results in a significant risk to the patient's safety.
- Pregnancy
- Infections that are considered, by the investigator, not possible to effectively manage whilst the patient is receiving LNP023 or rituximab.
- Use of prohibited treatment as outlined in Table 6-2 and Table 6-3 listing prohibited medications
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the patient's overall status, prevents the patient from continuing participation in the study.
- Please see Section 16.1 Appendix 1 for additional information on discontinuing treatment based on laboratory evidence of liver injury.

9.1.2 Discontinuation due to COVID-19

In the case that, a subject has a positive SARS-CoV-2 viral test or in the opinion of the investigator, presents COVID-19-related symptoms, discontinuation of study treatment will be discussed and agreed on a case by case basis by the investigator in consultation with Novartis, as applicable. For discontinued subjects, where possible, the upcoming assessments should be performed as per the assessment schedule.

9.1.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until the time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.4 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.5 Study stopping rules

Sponsor will review emergent safety reports on an ongoing basis to react as soon as there is a possibility that a stopping rule could apply. The sponsor will review all SAE as individual cases and will also be able to review summaries of non-serious adverse events for patterns and trends, and will first exclude any events determined to be clearly not related to study treatments (e.g., SAE which occurred during the pre-treatment screening period, or disease-related SAE expected in the population under study).

Enrollment in the study and dosing of affected subject(s) with study treatments will be paused if any of the following occurs during the study:

- One fatal or life-threatening SAE that is considered by the investigator as potentially related to the study treatments
- OR two or more SAEs that are considered by the investigator as potentially related to the study treatments

The study may resume following the safety review, if the investigator and sponsor are also in agreement. Restart of this clinical trial in such case will be documented by a substantial amendment and following approval by relevant health authorities.

9.1.6 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes her/his EOS visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the investigator or, in the event of an early study termination decision, the date of that decision. Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them.

All treated subjects should have a safety follow-up call conducted 30 days after end of treatment period (week 28), followed by post-treatment follow visits at week 37 and week 53. The information collected will be kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3 and SOM. Documentation of attempts to contact the subject should be recorded in the source documentation.

Continuing care should be provided by the investigator and/or referring physician after the EOS visit as per local standard of care.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade
   mild: usually transient in nature and generally not interfering with normal activities
   moderate: sufficiently discomforting to interfere with normal activities
   severe: prevents normal activities
2. its relationship to the study treatment . If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdrawn

6. its outcome: not recovered/not resolved; recovered/resolved;, recovered/resolved with sequelae; fatal; or unknown

Conditions that were already present at the time of informed consent should be recorded in medical history of the subject.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days (or 5 half-lives or end of study visit, whichever is longer) following the last dose of study treatment.

Information about adverse drug reactions for the investigational drug can be found in the IB.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in subjects with the underlying disease.

Follow the instructions found in the Site Operations Manual for data capture methodology regarding AE collection for subjects that fail screening.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the subject's general condition

  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit must be reported to sponsor safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

Screen Failures

SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to sponsor.

Definition of Run-In Failures

A subject who is screened but not randomized/treated after the run-in period. SAEs collected between time subject signs ICF until time that subject is determined to be a run-in failure.

Definition of Baseline Failures

A subject who performs baseline assessments but not randomized/treated after baseline visit. SAEs collected between time subject signs ICF until time that subject is determined to be a baseline failure.

Randomized

SAEs collected between time subject signs ICF until 30 days after the subject has discontinued study treatment or completed their last study visit.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period after the last study visit should only be reported to sponsor Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Pregnancies

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and contributing factors are recorded on the appropriate CRFs

Please refer to Table 16-1 in Section 16.1 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-2. Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.
- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.

- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section , Section 9.1.1), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
  - These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information and procedures performed must be recorded as appropriate in the CRF.

Refer to the SOM for additional details.

10.2.2 Renal safety monitoring

Renal safety monitoring is already performed as part of the study endpoints.

10.2.3 Data Monitoring Committee

There is no Data Monitoring Committee (DMC) for this trial.

10.2.4 Infection surveillance

All infections that develop during the study will be reported as AEs. Investigators are requested to specifically enquire about signs and symptoms of infections at each visit, in particular for encapsulated bacteria. Beta-lactam, macrolide and quinolone antibiotics can be used for prophylactic treatment in accordance with local practice. A suggested regimen would include Ciprofloxacin 500 mg p.o. b.i.d. x 14 days followed by long term treatment with Penicillin V 500 mg p.o. b.i.d. or erythromycin 500 mg p.o b.i.d. for patients intolerant to penicillin V while on LNP023. Choice and regimen of antibiotic treatments needs to be adjusted to local requirements and guidelines. Other additional evaluations will be performed at the discretion of the investigator.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The investigator must certify that the data entered are complete and accurate. Certain data may be captured via other source documentation (such as safety laboratory data report) and then transcribed, uploaded or transferred into the system. This, and any additional data treated in this manner, will be source data verified by the study monitor per the monitoring plan and the location of source data (i.e., source, paper or a local electronic system) will be documented prior to study start in the Data Quality Plan. The system has the ability to illustrate when a document has been entered from another source. When using an electronic source record as the original point of data capture, there is no additional data entry step for the site for data collected directly into the application; rather, the electronic source record directly populates the study database. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to sponsor. Remote monitoring of the original electronic source records will take place, however on-site monitoring inspections will continue to take place in order to review data entry of source documentation directly captured on paper and transcribed into the system, to ensure protocol adherence, to assess site operational capabilities, and to perform other monitoring activities that cannot be performed remotely.

After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Randomization codes and data about all study treatment (s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis at specific timelines.

Each occurrence of a code break via IRT for LNP023 regimens will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis or delegated CRO representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/delegated CRO/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

The analysis will be conducted on all subject data at the time when an interim analysis occurs or when the trial ends.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

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12.1 Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

The full analysis set (FAS) will include all randomized subjects.

The safety analysis set will include all subjects that received any study drug.

The PK analysis set will include all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data.

The PD analysis set will include all subjects that receive any study treatment and no protocol deviations with relevant impact on PD/efficacy data.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including UPCR, PLA2R CCI will be summarized descriptively by treatment group for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be summarized separately by system organ class and preferred term, by treatment group.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

The duration of exposure in weeks to study treatment will be summarized by means of descriptive statistics using the safety set. Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.

12.4 Analysis of the primary endpoint(s)

The primary aim of the study is to assess the reduction in UPCR (measured in 24h urine) in LNP023 200 mg treated subjects compared with rituximab after 24 weeks of treatment.

In the LNP023 treatment groups patients are considered as under treatment whilst taking the treatment and 30 days after the last administration. In the Rituximab arm, patients are considered as under treatment if they received both injections, or 3 months after they received the single injection.

12.4.1 Definition of primary endpoint(s)

The primary endpoint of this study is the ratio between baseline UPCR and UPCR at 24 weeks of treatment measured in 24h urine. This endpoint will be log-normal transformed prior to analysis, as it is assumed to follow a log-normal distribution.

12.4.2 Statistical model, hypothesis, and method of analysis

To assess the primary objective, UPCR will be analyzed using a mixed model for repeated measures. The results will be back transformed and presented on the original scale.

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The following two criteria will be used to assess treatment efficacy:

- Statistically significant decrease (no worse than 55% increase) in UPCR at week 24 visit in LNP023 200 mg -treated subjects vs. rituximab-treated subjects at one-sided 10% level (i.e. H_0 : (ratio from BL in UPCR_LNP)/ (ratio from BL in UPCR_Ritux) $\geq$ 1.55)
- Estimated mean reduction in UPCR in LNP023 200 mg-treated subjects better than 10% increase vs rituximab-treated subjects (i.e. (ratio from BL in UPCR_LNP)/ (ratio from BL in UPCR_Ritux) < 1.1)

12.4.3 Handling of missing values/censoring/discontinuations

All subjects with at least one post baseline measurement of UPCR in 24h urine will be used in the analysis. The primary Mixed effect Model Repeat Measurement (MMRM) model implicitly imputes missing data under a missing at random assumption.

12.4.4 Supportive analyses

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12.5 Analysis of secondary endpoints

Details of the statistical methodologies for the secondary endpoints will be described in the SAP. Graphical presentation of the data will be performed where applicable.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Responder assessment

The proportion of responders in the rituximab and LNP023 200 mg will be determined and compared between treatment groups. A subject is a complete responder, if he/she shows complete remission (i.e. proteinuria $\leq$ 0.3 g/24h) after 24 weeks of treatment. Similarly, a subject whose proteinuria is > 0.3g/24h and $\leq$ 3.5 g/24h (partial remission) after 24 weeks of treatment will be considered a partial responder. Only subjects who discontinue treatment early will be considered as non-responder in this analysis.

eGFR Change from Baseline

The change in eGFR applying the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation from baseline to 24 weeks of treatment will be evaluated and reported.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used. All tables will be presented by treatment group.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The on-treatment period in the LNP023 treatment groups lasts from the date of first administration of study treatment to 30 days after the date of the last actual administration of any study treatment. The on-treatment period in the rituximab treatment group lasts from the first administration to 6 months after the date of the second administration. Subjects who received a single rituximab infusion are considered under treatment until 3 months after this single infusion.

Adverse events

All information obtained on adverse events will be displayed by treatment group and subject.

The number (and percentage) of subjects with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term;
- by treatment, primary system organ class, preferred term and maximum severity;
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation.

The number (and proportion) of subjects with adverse events of special related to identified and potential risks (i.e. systemic bacterial infection, anaemia, abnormalities of thyroid function and testicular symptoms and / or abnormalities of reproductive hormone levels) will be summarized by treatment.

A subject with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Adverse events which will be counted for a specific treatment period are those which are treatment-emergent. These events are those with an onset after the start of the treatment period, or which were present prior to the start of the treatment period but increased in severity, changed from being not suspected to being suspected of study drug relationship, or developed into SAEs after the start of the treatment period.

Heatmaps will be provided by treatment group displaying the on- and off-set of the most severe AE in a subject over time.

Vital signs

Summary statistics will be provided on all vital signs data by treatment and visit/time.

12-lead ECG

PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each subject during the study. ECG data will be read and interpreted (locally). Summary statistics will be provided on all ECG data by treatment and visit/time.

Clinical laboratory evaluations

Summary statistics will be provided on all laboratory data by treatment and visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

12.5.3 Pharmacokinetics

Descriptive summary statistics will be provided by dose and visit/sampling time point, Commercially Confidential Information

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum.
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Table 12-1 Non-compartmental pharmacokinetic parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1)
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1)
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
T1/2	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives

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12.6 Analysis of exploratory endpoints

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12.6.1 Biomarkers

For the biomarker analyses only the LNP023 CCI 200mg –treated and rituximab-treated subjects will be included.

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The effect on the treatment over time will be assessed

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A scatterplot of UPCR from first morning void and 24h urine UPCR at each visit will be performed to assess UPCR from first morning void as a monitoring marker.

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The disease severity at baseline and the relationship with anti-PLA2R will be assessed graphically.

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12.7 Interim analyses

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12.8 Sample size calculation

12.8.1 Primary endpoint(s)

A total of approximately 52 subjects will be recruited into the study: approximately 24 on LNP023 200 mg, approximately 24 on rituximab Commercially Confidential Information This number is based on several assumptions: the assumed treatment effect, the variability of the primary endpoint log UPCR as well as on the assumed drop-out rate of 17% (i.e. 9 subjects).

With data from 40 subjects for the analysis of the primary efficacy variable, there is 80% chance that the predefined efficacy criteria (Section 12.4.2) will be met, assuming the true reduction of UPCR of LNP023 200 mg vs. rituximab is 8% (i.e. (ratio from BL in UPCR_LNP)/ (ratio from BL in UPCR_Ritux) = 0.92). If the true increase of LNP023 200 mg vs. rituximab is 55% (i.e. (ratio from BL in UPCR_LNP)/ (ratio from BL in UPCR_Ritux) = 1.55) the chance of meeting the efficacy criteria is around 14%.

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13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to sponsor monitors, auditors, sponsor Quality Assurance representatives, designated agents of sponsor, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform sponsor immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the sponsor publication policy including authorship criteria, please refer to the sponsor publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Sponsor maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and sponsor systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written sponsor processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by sponsor, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, sponsor should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

References are available upon request

Acevedo Ribó M, Ahijado Hormigos FJ, Díaz F, et al (2016) IgG4-related disease and idiopathic membranous nephropathy: "The clothes do not make the man". Clin. Nephrol. p. 345-348.

Alanee SR, McGee L, Jackson D, et al (2007) Association of serotypes of Streptococcus pneumoniae with disease severity and outcome in adults: an international study. Clin. Infect. Dis. p. 46-51.

Baker PJ, Ochi RF, Schulze M, et al (1989) Depletion of C6 prevents development of proteinuria in experimental membranous nephropathy in rats. Am. J. Pathol. p. 185-94.

Borza DB (2016) Alternative Pathway Dysregulation and the Conundrum of Complement Activation by IgG4 Immune Complexes in Membranous Nephropathy. Front Immunol p. 157.

Bryant KA, Frenck R, Gurtman A, et al (2015) Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine in adults 18-49 years of age, naive to 23-valent pneumococcal polysaccharide vaccine. Vaccine p. 5854-5860.

Cattran DC, Brenchley PE (2017) Membranous nephropathy: integrating basic science into improved clinical management. Kidney Int. p. 566-574.

Cattran DC, Kim ED, Reich H, et al (2017) Membranous Nephropathy: Quantifying Remission Duration on Outcome. J. Am. Soc. Nephrol. p. 995-1003.

Cybulsky AV, Quigg RJ, Salant DJ (1986) The membrane attack complex in complement-mediated glomerular epithelial cell injury: formation and stability of C5b-9 and C5b-7 in rat membranous nephropathy. J. Immunol. p. 1511-6.

Dahan K, Debiec H, Plaisier E, et al (2017) Rituximab for Severe Membranous Nephropathy: A 6-Month Trial with Extended Follow-Up. J. Am. Soc. Nephrol. p. 348-358.

Endo M, Fuke Y, Tamano M, et al (2004) Glomerular deposition and urinary excretion of complement factor H in idiopathic membranous nephropathy. Nephron Clin Pract p. c147-53.

Fervenza FC, Canetta PA, Barbour SJ, et al (2015) A Multicenter Randomized Controlled Trial of Rituximab versus Cyclosporine in the Treatment of Idiopathic Membranous Nephropathy (MENTOR). Nephron p. 159-68.

Fogo AB, Lusco MA, Najafian B, et al (2015) AJKD Atlas of Renal Pathology:Membranous Nephropathy p. 66 (3) pp e15-7.

Gossger N, Snape MD, Yu LM, et al (2012) Immunogenicity and tolerability of recombinant serogroup B meningococcal vaccine administered with or without routine infant vaccinations according to different immunization schedules: a randomized controlled trial. JAMA p. 573-82.

Hoxha E, Thiele I, Zahner G, et al (2014) Phospholipase A2 receptor autoantibodies and clinical outcome in patients with primary membranous nephropathy. J. Am. Soc. Nephrol. p. 1357-66.

KDIGO Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group (2012) KDIGO Clinical Practice Guidelines for Glomerulonephritis p. 2, pp139-274.

Keyserling H, Papa T, Koranyi K, et al (2005) Safety, immunogenicity, and immune memory of a novel meningococcal (groups A, C, Y, and W-135) polysaccharide diphtheria toxoid conjugate vaccine (MCV-4) in healthy adolescents. Arch Pediatr Adolesc Med p. 907-13.

Konar M, Granoff DM (2017) Eculizumab treatment and impaired opsonophagocytic killing of meningococci by whole blood from immunized adults. Blood p. 891-899.

Kościelska-Kasprzak K, Bartoszek D, Myszka M, et al (2014) The complement cascade and renal disease. Arch. Immunol. Ther. Exp. (Warsz.) p. 47-57.

Luo W, Olaru F, Miner JH, et al (2018) Alternative Pathway Is Essential for Glomerular Complement Activation and Proteinuria in a Mouse Model of Membranous Nephropathy. Front Immunol p. 1433.

Lönnbro-Widgren J, Ebefors K, Mölne J, et al (2015) Glomerular IgG subclasses in idiopathic and malignancy-associated membranous nephropathy. Clin Kidney J p. 433-9.

Ma H, Sandor DG, Beck LH (2013) The role of complement in membranous nephropathy. Semin. Nephrol. p. 531-42.

MacNeil JR, Cohn AC, Farley M, et al (2011) Current epidemiology and trends in invasive Haemophilus influenzae disease--United States, 1989-2008. Clin. Infect. Dis. p. 1230-6.

Maillard N, Wyatt RJ, Julian BA, et al (2015) Current Understanding of the Role of Complement in IgA Nephropathy. J. Am. Soc. Nephrol. p. 1503-12.

Matsumoto M, Fukuda W, Circolo A, et al (1997) Abrogation of the alternative complement pathway by targeted deletion of murine factor B. Proc. Natl. Acad. Sci. U.S.A. p. 8720-5.

McFetridge R, Meulen AS, Folkerth SD, et al (2015) Safety, tolerability, and immunogenicity of 15-valent pneumococcal conjugate vaccine in healthy adults. Vaccine p. 2793-9.

McGrogan A, Franssen CF, de Vries CS (2011) The incidence of primary glomerulonephritis worldwide: a systematic review of the literature. Nephrol. Dial. Transplant. p. 414-30.

Merle NS, Church SE, Fremeaux-Bacchi V, et al (2015a) Complement System Part I - Molecular Mechanisms of Activation and Regulation. Front Immunol p. 262.

Merle NS, Noe R, Halbwachs-Mecarelli L, et al (2015b) Complement System Part II: Role in Immunity. Front Immunol p. 257.

Nester CM, Smith RJ (2013) Diagnosis and treatment of C3 glomerulopathy. Clin. Nephrol. p. 395-403.

NHS Commissioning through Evaluation available at <https://www.sps.nhs.uk/wp-content/uploads/2019/04/Spec-Comm-Drugs-Briefing-Spring-2019.pdf> (accessed on 1 June 2019)

Pourcine F, Dahan K, Mihout F, et al (2017) Prognostic value of PLA2R autoimmunity detected by measurement of anti-PLA2R antibodies combined with detection of PLA2R antigen in membranous nephropathy: A single-centre study over 14 years. PLoS ONE p. e0173201.

Rituximab SmPC (2019) Biogen. Rituxan (rituxiamb) 10 mg/mL solution for injection. Summary of Product Characteristics; 1-45

Salant DJ, Belok S, Madaio MP, et al (1980) A new role for complement in experimental membranous nephropathy in rats. J. Clin. Invest. p. 1339-50.

Skattum L, van Deuren M, van der Poll T, et al (2011) Complement deficiency states and associated infections. Mol. Immunol. p. 1643-55.

Slade C, Bosco J, Unglik G, et al (2013) Deficiency in complement factor B. N. Engl. J. Med. p. 1667-9.

Sridhar S, Greenwood B, Head C, et al (2015) Global incidence of serogroup B invasive meningococcal disease: a systematic review. Lancet Infect Dis p. 1334-46.

Tang L, Yao J, Kong X, et al (2017) Increasing prevalence of membranous nephropathy in patients with primary glomerular diseases: A cross-sectional study in China. Nephrology (Carlton) p. 168-173.

Thompson A, Cattran DC, Blank M, et al (2015) Complete and Partial Remission as Surrogate End Points in Membranous Nephropathy. J. Am. Soc. Nephrol. p. 2930-7.

Timmermans SA, Abdul Hamid MA, Cohen Tervaert JW, et al (2015) Anti-PLA2R Antibodies as a Prognostic Factor in PLA2R-Related Membranous Nephropathy. Am. J. Nephrol. p. 70-7.

Wetmore JB, Guo H, Liu J, et al (2016) The incidence, prevalence, and outcomes of glomerulonephritis derived from a large retrospective analysis. Kidney Int. p. 853-60.

Yang Y, Wang C, Jin L, et al (2016) IgG4 anti-phospholipase A2 receptor might activate lectin and alternative complement pathway meanwhile in idiopathic membranous nephropathy: an inspiration from a cross-sectional study. Immunol. Res. p. 919-30.

16 Appendices

Table 16-1 Definitions of Triggers, Actions and Follow-up requirements for liver events

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case (Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN – or 3 x ULN in the presence of bone pathology)	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality (investigate alternative etiologies)[a] • Record the AE and contributing factors (e.g. concomitant medication, medical history, laboratory value) in the appropriate eCRF	• ALT, AST, TBL, Alb, PT/INR, ALP, GGT, CK and GLDH (frequency at Investigator discretion) • Monitor for symptoms[b] • Report outcome[c]
ALT or AST		
> 8 × ULN	• Interrupt the study treatment • Hospitalize if clinically appropriate • Establish causality (investigate alternative etiologies)[a] • Study drug can be restarted only if alternative etiology is identified and liver enzymes return to baseline • Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	• ALT, AST, TBL, Alb, PT/INR, ALP and GGT (frequency at Investigator discretion) • Monitor for symptoms[b] • Report outcome[c]
> 3 × ULN and INR > 1.5 If elevated at baseline: > 2 x baseline or > 300 U/L (whichever occurs first)	• Interrupt the study treatment • Hospitalize if clinically appropriate • Establish causality (investigate alternative etiologies)[a] • Study drug can be restarted only if alternative etiology is identified and liver enzymes return to baseline • Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	• ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion)
> 5 to ≤ 8 × ULN If elevated at baseline: > 3 x baseline or > 300 U/L (whichever occurs first)	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality (investigate alternative etiologies)[a] • Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	• ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion)

Criteria	Actions required	Follow-up monitoring
> 3 × ULN to ≤ 5 × ULN (accompanied by symptoms)[b] If elevated at baseline: > 2 x baseline or > 300 U/L (whichever occurs first)	• Interrupt the study treatment • Hospitalize if clinically appropriate • Establish causality (investigate alternative etiologies)[a] • Study drug can be restarted only if alternative etiology is identified and liver enzymes return to baseline • Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	• ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion) • Monitor for symptoms[b] • Report outcome[c]
> 3 to ≤ 5 × ULN (patient is asymptomatic)[b] If elevated at baseline: > 2 x baseline or > 300 U/L (whichever occurs first)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the subject	• Investigator discretion • Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology) >3 x ULN if bone pathology is present	• Repeat LFT within 48 hours • If elevation persists, establish causality (investigate alternative etiologies)[a] • Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	• Investigator discretion • Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality (investigate alternative etiologies)[a] • Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	• ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at Investigator discretion) • Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)[b]	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the subject	• Investigator discretion • Monitor LFT within 1 to 4 weeks or at next visit

Criteria	Actions required	Follow-up monitoring
Jaundice	• Interrupt the study treatment • Hospitalize the subject • Establish causality (investigate alternative etiologies)[a] • Study drug can be restarted only if alternative etiology is identified and liver enzymes return to baseline • Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	• ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion) • Monitor symptoms[b] • Report outcome[c]
Any AE potentially indicative of a liver toxicity[d]	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality (investigate alternative etiologies)[a] • Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	• Investigator discretion

[a] Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

[b]Severe fatigue, malaise (general), abdominal pain (right upper quadrant), nausea, vomiting or rash with eosinophilia

[c]Resolved = return to Day 1 values; Condition unchanged = stable values at three subsequent monitoring visits at least 2 weeks apart; Condition deteriorated = values worsen or liver transplantation; and Fatal.

[d]These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms.

TBL: total bilirubin; ULN: upper limit of normal

Liver event guidance for CRF completion is available in the Site Operations Manual.