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LNP023

Clinical Trial Protocol CLNP023X2202 / NCT03832114

An open-label, non-randomized study on efficacy, pharmacokinetics, pharmacodynamics, safety and tolerability of LNP023 in two patient populations with C3 glomerulopathy

Document type:	Amended Protocol Version
EUDRACT number:	2017-000889-29
Version number:	v03 (Clean)
Clinical Trial Phase:	II
Release date:	07-Feb-2020

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

ACE	Angiotensin converting enzyme
ACEi	Angiotensin converting enzyme inhibitor
AE	adverse event
aHUS	atypical hemolytic uremic syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AP	Alternative pathway
ARB	Angiotensin receptor blocker
AST	aspartate aminotransferase

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BUN	blood urea nitrogen
C3	Component 3
C3G	Component 3 glomerulopathy
C3GN	C3 glomerulo nephritis
CAP	Complement Alternative Pathway
CDRD	Complement driven renal diseases
CK	creatinine kinase
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology
CLr	Renal plasma clearance
CMO&PS	Chief Medical Office & Patient Safety
COA	Clinical outcome assessments
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTC	Common Toxicity Criteria
CTT	Clinical trial team
CV	coefficient of variation
DDD	Dense deposit disease
DDE	Direct data entry
DHT	Dihydrotestosterone
ECG	Electrocardiogram
eCRF	Electronic case report forms
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
EMA	European Medicine Agency
EOS	End of study
eSource	Electronic Source
ESRD	End-stage renal disease

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FDA	Food and Drug Administration

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GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLP	Good laboratory practices
h	hour
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
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
IgAN	IgA nephropathy
INR	International Normalized Ratio
IRB	Institutional Review Board

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KDIGO	Kidney Disease Improving Global Outcomes
Kg	kilogram
LDH	lactate dehydrogenase
LFT	Liver function test

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MAR	Missing at random
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)

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MMRM	Mixed model repeated measures
MN	Membranous nephropathy

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PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PNH	Paroxysmal nocturnal hemoglobinuria
POC	Proof of concept
ppm	parts per million
PT	prothrombin time
RBC	red blood cell(s)
RNA	Ribonucleic acid
SAE	serious adverse event
SAP	Statistical analysis plan

sCR	serum creatinine
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOM	Site Operations Manual
SOP	Standard operation procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
TMA	Thrombotic microangiopathy

UA	Urine albumin
UACR	Urine albumin to creatinine ratio
Ue	Urinary excretion
ULN	upper limit of normal
UP	Urine protein
UPCR	Urine protein to creatinine ratio
VLDL-C	Very low density lipoprotein-cholesterol
WBC	white blood cell(s)
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Any drug(s) (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
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.
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)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up) which applies across all arms of a study.
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.
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug,” "Investigational Medicinal Product," or “test substance”
Patient	An individual with the condition of interest
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
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
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	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	CLNP023X2202
Full Title	An open-label, non-randomized study on efficacy, pharmacokinetics, pharmacodynamics, safety and tolerability of LNP023 in two patient populations with C3 glomerulopathy
Brief title	Study on efficacy and safety of LNP023 in C3 glomerulopathy patients transplanted and not transplanted
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 assess the clinical efficacy, pharmacodynamics, safety, tolerability and pharmacokinetics of LNP023 in patients with C3 glomerulopathy (C3G) and to evaluate the effect of different doses of LNP023 on complement biomarkers Commercially Confidential Information C3G patients who have not received a kidney transplant and have reduced C3 blood levels will be included in Cohort A of this study; C3G patients who have received a kidney transplant and have C3G recurrence will be included in Cohort B.
Primary Objective(s)	• Cohort A: To evaluate the efficacy of LNP023 in reducing proteinuria at Week 12 • Cohort B: To assess histopathological changes in kidney biopsies at Week 12
Secondary Objectives	Commercially Confidential Information • All Cohorts: To assess the relationship between LNP023 dose and proteinuria • All Cohorts: To assess the effect of LNP023 on renal function • All Cohorts: To assess the effect of LNP023 on alternative complement pathway hyperactivity • All Cohorts: To assess the safety and tolerability of LNP023 • All Cohorts: To assess the plasma and urine pharmacokinetics of LNP023 in patients with C3G • Cohort B: To evaluate the efficacy of LNP023 in reducing proteinuria at Week 12

Study design	The study is a non-confirmatory, open-label, two cohort single arm, non-randomized, study evaluating the efficacy, safety, tolerability, pharmacokinetics, pharmacodynamics and dose/biomarker relation of LNP023 in two patient populations: non-transplanted C3G patients with reduced C3 serum levels Commercially Confidential Information enrolled in Cohort A and patients who have undergone kidney transplantation and have C3G recurrence, enrolled in Cohort B. Cohort B will start in parallel to Cohort A. On completion of Treatment period Commercially Confidential Information the patient can: - roll-over directly in the extension study or CCI proceed to follow-up period. Commercially Confidential Information
Population	Approximately 15 C3G patients (male or female) with native kidneys and with reduced serum C3 levels will be enrolled in Cohort A to ensure that 12 patients complete the study in this Cohort. Approximately 12 C3G kidney transplanted patients with C3G recurrence (male or female) will be enrolled in Cohort B to ensure that at least 10 complete the study in this Cohort.
Key Inclusion criteria	**Part 1** Cohort A • Patients (females and males 18 years or older in age) must have C3G as confirmed by renal biopsy within twelve months prior to enrollment (confirmation by the Investigator is required). • C3G patients with reduced C3 at screening CCI are eligible for this study. • Estimated GFR (using the CKD-EPI formula) ≥30 mL/min per 1.73 m^2 for patients on a maximum recommended or maximum tolerated dose of an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB). • UPCR ≥ 100 mg/mmol sampled from first morning void (or ≥ 1 g/24h total urinary protein excretion from a 24h urinary collection during run-in) at run-in (Visit 20) or at baseline (Visit 30). • Any antiproteinuric medication (e.g., angiotensin converting enzyme inhibitors, angiotensin II receptor blockers) must be at a stable dose for at least 30 days prior to treatment start. • Commercially Confidential Information

	Commercially Confidential Information Cohort B • Patients (females and males 18 years or older in age) must have C3G recurrence after transplantation as confirmed by renal biopsy after transplantation within twelve months prior to enrollment (confirmation by the Investigator is required). Commercially Confidential Information • Normal or elevated urinary protein excretion at screening or at baseline (Visit 30). • Commercially Confidential Information • Commercially Confidential Information • If applicable, induction treatment after allotransplantation needs to be completed >30 days before inclusion. Any commercially available induction agent is permitted. • Patients need to be on a stable dose of immunosuppressive regimen prior to Day 1. Any commercially available treatments are allowed for this purpose (if not prohibited as per protocol). • Transplantation of a kidney allograft >30 days before screening • No histologic signs of allorejection

Key Exclusion criteria	Cohort A • Known family history or known presence of long QT syndrome or Torsades de Pointes. • Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test • Donation or loss of 400 mL or more of blood within eight (8) weeks prior to initial dosing, or longer if required by local regulation. • Plasma donation (>200 mL) within 30 days prior to first dosing. • Patients who cannot receive vaccinations against *N. meningitidis*, *S. pneumoniae*, or *H. influenzae*. • Use of other investigational drugs at the time of enrollment, or within 5 half-lives, or within 30 days of screening, whichever is longer; or longer if required by local regulations. Cohort B • Known family history or known presence of long QT syndrome or Torsades de Pointes. • Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test. Commercially Confidential Information • Patients who cannot receive vaccinations against *N. meningitidis*, *S. pneumoniae*, or *H. influenzae*. • Use of other investigational drugs at the time of enrollment, or within 5 half-lives, or within 30 days of screening, whichever is longer; or longer if required by local regulations.
Study treatment	LNP023
Efficacy assessments	Cohort A: Reduction from baseline in UPCR at Week 12 Cohort B: Change from baseline in C3 Deposit Score (based on immunofluorescence microscopy)
Pharmacodynamic assessments	The secondary variables supporting the secondary objective to assess the effect of LNP023 on renal function are UA, UACR, UP, UPCR, serum creatinine, creatinine clearance, eGFR (using the CKD-EPI formula), hematuria, blood levels of Bb.
Pharmacokinetic assessments	Plasma PK parameters: Non-compartmental analysis and calculation of PK parameters based on total LNP023 concentrations, including but not limited to Tmax, Cmax, AUClast and AUCtau, as well as Ctrough (Cmin) after multiple doses Urine PK parameters: Non-compartmental analysis of parameters including total cumulative urinary excretion (Ue) and renal plasma clearance (CLr) of LNP023.
Key safety assessments	ECG, vital signs, safety laboratory assessments CCI , AEs and SAEs.

Other assessments	Commercially Confidential Information
Data analysis	Statistical Analysis: The data analysis includes data generated from Screening, Treatment period CCI and safety Follow-up periods. Commercially Confidential Information Cohort A The primary variable for assessing the effect of LNP023 is the log ratio to baseline UPCR derived from the 24h urine collections at Week 12. A mixed model repeated measures (MMRM) will be fitted to the log ratio to baseline UPCR values over time. The model will include the log ratio to baseline UPCR as the dependent variable, time point (as study day relative to the start of study treatment) as a fixed effect, and baseline log transformed UPCR as a fixed covariate. Baseline is defined to be the 24-hour urine collection on Day -1 to Day 1. An unstructured covariance matrix will be used. Results from this modelling will be presented as the estimated mean value of log UPCR at week 12 together with the 80% confidence interval. The results will be back transformed to provide the geometric mean and their 80% CIs on the original scale. Cohort B The primary variable for assessing the histopathological changes in kidney biopsies is Week 12 change from baseline in C3 Deposit Score. The Wilcoxon signed rank test will be used for C3 Deposit Score data at Week 12 to compare the median difference of change from baseline. The Hodges-Lehmann estimate and 80% confidence interval for the median difference will be provided. More details on Statistical analysis will be discussed in detail in the SAP.
Key words	C3G, C3 glomerulopathy

1 Introduction

1.1 Background

Approximately 10% of the population worldwide is affected by chronic kidney disease (CKD) and millions die each year due to the lack of available or effective treatment (Webster et al 2017). Over 2 million people have end-stage renal disease (ESRD) (Jha and Rathi 2013) and are dependent on dialysis for their survival or have undergone kidney transplantation (Couser et al 2011). CKD results from renal diseases with different underlying molecular mechanisms and with a wide range of rates of progression. Many of the renal diseases that progress to CKD and ESRD are characterized by inflammation and involve dysregulation of the complement system.

The complement pathway is important for innate and adaptive immunity. Inherited and acquired dysregulation of the complement alternative pathway (AP) plays an important role in many renal diseases, almost all of which show signs of complement AP dysregulation in renal biopsies (Mathern and Heeger 2015). Complement driven renal diseases (CDRD) for which there is strong scientific evidence for complement AP dysregulation include component 3 glomerulopathy (C3G) (Barbour et al 2013), IgA nephropathy (IgAN) (Floege et al 2014, Maillard et al 2015) and membranous nephropathy (MN) (Ruggenenti et al 2007). There are limited (mostly symptomatic) therapies available to treat these diseases, which generally progress to CKD and ESRD. In some patients, the progression towards ESRD takes a decade or two, but for a subset of patients the rate of progression is much faster, reducing the quality of life and shortening life expectancy. The risk of these diseases returning after kidney transplantation is also very high.

There is a high unmet medical need for new therapies to treat CDRD and therapies that target the complement system represent a promising approach. Novartis is investigating LNP023, a novel oral factor B inhibitor. Factor B (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 is being developed to address the unmet need in patients with CDRD and will initially be developed for the treatment of C3G, IgAN and MN, all orphan diseases.

C3 glomerulopathy is a rare inflammatory kidney disease caused by genetic mutations in the alternative pathway of the complement system, or by autoantibodies (C3Nefs) that stabilize the C3 convertases that leads to dysregulation of the alternative pathway with consumption of the C3 of the complement system and coating of glomeruli with C3 fragments, responsible for inflammation and destruction of renal tissue.

The diagnosis of C3G is established by renal biopsy showing dominant C3 deposition. In most cases (60%) autoantibodies are found that stabilize C3 convertase but approximately 40% of patients have mutations in the genes for factor H, FB, or C3, or abnormal factor H related proteins (Nester and Smith 2016, Goodship et al 2017). Worldwide, the prevalence of C3G is 8-12 per million (Thomas et al 2014) and the annual incidence is 1-2 per million per year, with an estimated 3,910 patients in the United States (US) and 3,222 patients in the Europe Union (EU) (Riedl et al 2017).

C3G exists in two forms: C3 glomerulonephritis (C3GN) and dense deposit disease (DDD) with a ~3:1 ratio in prevalence (refer to Table 1-1), respectively. DDD is mainly a pediatric disease, with an average age of diagnosis of 12 years (range 8-20), while the more common form C3GN mainly affects adults (average age at diagnosis 26, range 12-53) (Medjeral-Thomas et al 2014). Diagnosis is based on renal biopsy which demonstrates glomeruli that contain C3 fragments (iC3b, C3c and C3dg) in abundance without immunoglobulin (Pickering et al 2013). Glomerular histology may show a range of features: membranoproliferative, mesangial proliferative, or endocapillary proliferative and there may be glomerular crescents as well. C3G patients also have reduced serum levels of C3, FB and properdin and elevated levels of Ba, Bb, C3a, C3d and C5b9 (Zhang et al 2014).

Although some patients with C3G may have mild disease with asymptomatic micro-hematuria and/or proteinuria, the majority of patients have severe, rapidly progressive disease with a nephritic or nephrotic syndrome and renal impairment. In fact, 33% of C3G patients progress to ESRD within 6 years and 50% of patients progress to ESRD within 10 years (Medjeral-Thomas et al 2014). The disease often recurs after renal transplantation (~80% risk), limiting the use of this modality, and thereby reducing the life expectancy of C3G patients. Patients often experience fatigue and exercise intolerance due to the underlying inflammation and anemia often accompanied by proteinuria, hematuria, hypertension, and sometimes severe edema (Table 1-1). For these reasons, patients also experience detrimental and life-altering changes in their psychological, social, educational and vocational development. Some patients with C3G also develop drusen, which is a form of macular degeneration that can impair vision (Savige et al 2016). There is also an increased risk for thrombotic microangiopathy (TMA) in patients with C3G and their descendants. In a French study for example, 17% of C3G patients developed TMA after transplantation (Servais et al 2012).

There is currently no approved treatment for C3G. Steroids and supportive treatment using angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are employed with very limited effectiveness. Recommendations from a "Kidney Disease: Improving Global Outcomes" (Couser et al 2011) Controversies Conference have been published recently (Goodship et al 2017). The report provides treatment approaches for the practical management of C3G patients in the absence of specific therapy. These approaches are primarily based on expert opinion with limited support from retrospective studies. With the awareness of the importance of AP for C3G disease, treatment with eculizumab has been tried in an increasing number of patients. Eculizumab is a humanized monoclonal antibody that inhibits the cleavage of C5 and the formation of the terminal MAC (C5b-9). It is approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS). Despite the fact that eculizumab does not reduce AP activation it seems to ameliorate symptoms in ~50% of patients with C3G (Bomback and Radhakrishnan 2014, Bomback et al 2012) confirming involvement of the complement pathway in this disease. However, eculizumab blocks terminal complement activation. Therefore, patients may have increased susceptibility to infections especially with encapsulated bacteria (Soliris EU SMPC). By contrast, LNP023 is a specific inhibitor of the AP pathway and as such should provide similar or greater efficacy in C3G patients with an improved safety profile. That is, the classical and lectin complement pathways remain functional in the presence of LNP023 and therefore should provide a lower risk of infection. Indeed, data supporting an intact serological response

to Neisseria infection during AP-blockade and a drastically reduced response during C5-blockade were recently presented (Konar and Granoff 2017).

Table 1-1 Clinical presentation and outcome of patients with dense deposit disease and C3 glomerulopathy

Clinical presentation / outcome	Dense deposit disease	C3 glomerulopathy
Prevalence (ppm)	1-2	7-10
Incidence (ppm/year)	0.2-0.4	0.8-1.6
Pediatric onset (<16 years)	43-70 %	25-54 %
Mean age at onset (years)	19 ± 18	30 ± 19
Clinical presentation		
Nephrotic syndrome	38-43 %	27-44 %
Micro-hematuria	76-84 %	65 %
Arterial hypertension	21-60 %	40 %
Impaired renal function (>1.5 mg/dL creatinine)	29 %	50 %
Low C3 (<75 mg/dL)	59-79 %	40-48 %
Long-term outcome		
Average duration to end-stage renal disease (years)	10 ± 11	11 ± 10
Estimated risk of recurrence of disease after kidney transplantation*	70-90%	60-80%

Table modified from (Riedl et al 2017). *Data based on limited number of studies (Salvadori and Bertoni 2016)

There is a clear unmet medical need in this orphan condition for which there is no approved therapy and which often exhibits a rapidly progressive course leading to end stage renal disease, a dramatic reduction in life expectancy and a highly negative impact on the quality of life.

1.2 Purpose

The purpose of this study is to assess the clinical efficacy, pharmacodynamics, safety, tolerability and pharmacokinetics of LNP023 in patients with C3 glomerulopathy (C3G) and to evaluate the effect of different doses of LNP023 on complement biomarkers CCI . C3G patients who have not received a kidney transplant and have reduced C3 blood levels will be included in Cohort A, C3G patients who have received a kidney transplant and have C3G recurrence will be included in Cohort B.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• **Cohort A:** To evaluate the efficacy of LNP023 in reducing proteinuria at Week 12	• Ratio to baseline of Urine Protein to Creatinine concentration Ratio (UPCR) derived from 24h urine collection.
• **Cohort B:** To assess histopathological changes in kidney biopsies at Week 12	• Change from baseline in C3 Deposit Score (based on immunofluorescence microscopy).
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• **All Cohorts:** To assess the relationship between LNP023 dose and pharmacodynamic biomarkers	• Biomarker levels of blood Bb
• **All Cohorts:** To assess the relationship between LNP023 dose and proteinuria	• 24h urine UPCR and UACR.
• **All Cohorts:** To assess the effect of LNP023 on renal function	• (i) change in and (ii) evolution of: urinary albumin (UA), urinary protein (UP) excretion; urine albumin to creatinine ratio (UACR) urine protein to creatinine ratio (UPCR), serum creatinine, estimated glomerular filtration rate (eGFR, using CKD-EPI formula), creatinine clearance, hematuria
• **All Cohorts:** To assess the effect of LNP023 on alternative complement pathway hyperactivity	• Blood level of C3.
• **All Cohorts:** To assess the safety and tolerability of LNP023	• ECG parameters, vital signs, safety laboratory assessments CCI , AEs and SAEs.
• **All Cohorts:** To assess the plasma and urine pharmacokinetics of LNP023 in patients with C3G	• Plasma: Non-compartmental parameter analysis related to total drug, including but not limited to Cmax, Tmax, AUClast, AUCtau and Ctrough (Cmin) after the first dose on Day 7, Day 14, Day 21 and Day 28, as well as Cmin on Days 92, and 99 or 176 and 183 . • Urine: Non-compartmental parameters, including but not limited to total cumulative urinary excretion (Ue) and renal plasma clearance (CLr).
• **Cohort B:** To evaluate the efficacy of LNP023 in reducing proteinuria at Week 12	• Ratio to baseline of UPCR and UACR derived from 24h urine collection.

Objective(s)	Endpoint(s)

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3 Study design

The study is a non confirmatory, open-label, two cohort single arm, non-randomized study evaluating the efficacy, safety, tolerability, pharmacokinetics, pharmacodynamics and dose/biomarker relation of LNP023 in two patient populations: non-transplanted C3G patients with reduced C3 serum levels (<0.90 x lower limit of the lab normal range), enrolled in Cohort A and patients who have undergone kidney transplant and have C3G recurrence, enrolled in Cohort B. Cohort B will start in parallel to Cohort A.

Cohort A

Approximately 15 patients will be enrolled in Cohort A to ensure that at least 12 patients complete the study in this cohort.

The study consists of (refer to Figure 3-1):

- A screening period that lasts up to 60 days and it is made up by a screening visit and a run-in period

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  During the run-in period, first morning void urine collection will be performed one time. It may be substituted by a 24h urine collection. A renal biopsy may be taken at any time during the screening period to confirm C3G diagnosis, if the most recent biopsy is older than 12 months.
- A baseline period of about 30 days, made up by two visits. During this period baseline values for key complement biomarkers, as per objectives, and efficacy related proteinuria will be established. Patients during baseline should be under stable doses of supportive therapy (antihypertensive and antiproteinuric therapy, e.g., angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, Commercially Confidential Information as per KDIGO guidelines; KDIGO 2012).

  Commercially Confidential Information Last baseline visit will be performed the day before first dosing.
- Treatment period of 12 weeks CCI

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- Follow-up period: A Commercially Confidential Information 12 weeks of safety follow-up without treatment. At the end of Treatment period if the Investigator does not deem it to be clinically beneficial for the patient to continue treatment, or if a patient does not want to continue treatment, the patient will enter the follow-up period.

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- A safety follow-up period of 12 weeks, without treatment, will follow. There will be 3 outpatient visits on Days 113, 127 and 155 Commercially Confidential Information

An end-of-study (EOS) visit is scheduled on Day 183

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Patients will remain on their supportive therapy, i.e. ACEi and/or ARB or other antihypertensive therapy, Commercially Confidential Information for the duration of the trial. To be dosed, patients must have been on stable therapy with an ACEi and/or ARB,

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During the treatment period, no change in medication is allowed except for safety reasons.

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Patients must receive vaccinations against *N. meningitidis*, *S. pneumoniae* and *H. influenzae* prior to first LNP023 dosing. Commercially Confidential Information

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Efficacy in terms of proteinuria and individual clinical response to various pharmacodynamic markers as well as pharmacokinetics will be assessed over the 12 week treatment period (refer to Table 8-1 and Table 8-2 the assessment schedule for detailed sampling time).

In this context, proteinuria will be assessed by collecting 24-h urine and first morning void urine to assess the change in and evolution of: UA and UP excretion, UACR and UPCR, creatinine clearance and hematuria.

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Safety monitoring includes the following assessments for each visit during Treatment period CCI and alerts will be set up for abnormal values to be reported immediately to Investigator and Sponsor:

- Renal function surveillance including serum creatinine, eGFR (using the CKD-EPI formula), hematuria, UA, UACR and UPCR assessments (refer to Section 8.3)
- Blood pressure (refer to Section 8.4.4.2)

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- 12-lead ECG (PR interval, QRS duration, heart rate, RR, QT, QTcF, refer to Section 8.4.2)
- Infection surveillance (refer to Section 10.2.3)
- Liver safety (ALT, AST, ALP, TBL, PT/INR, γGT levels, refer to Section 10.2.1)
- Hematology and blood chemistry parameters (refer to Section 8.4.1)
- Vital signs (refer to Section 8.4.4)
- Physical examination (refer to Section 8.4.7)
- AEs and SAEs recording (refer to Section 10)

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Cohort B

Approximately 12 patients will be enrolled in Cohort B to ensure that at least 10 patients complete the study in this Cohort.

The study consists of (refer to Figure 3-3):

- A screening period that lasts up to 60 days and consists of a screening visit and a run-in period.

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  During the run-in period first morning void urine collection will be performed one time. It may be substituted by a 24h urine collection. A renal biopsy may be taken at any time during the run-in period as baseline, if the most recent biopsy is older than 3 months.
- A baseline period of about 30 days, made up by two visits. During this period baseline values for key complement biomarkers, as per objectives, and efficacy related proteinuria will be established. Patients during baseline should be under stable doses of supportive therapy (antihypertensive and antiproteinuric therapy, e.g., angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, CCI as per KDIGO guidelines KDIGO 2012).

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  Last baseline visit will be performed the day before dosing.
- Treatment period of 12 weeks CCI :

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- Follow-up period: A Commercially Confidential Information 12 weeks of safety follow-up without treatment. At the end of Treatment period if the Investigator does not deem it to be clinically beneficial for the patient to continue treatment, or if a patient does not want to continue treatment, the patient will enter the follow-up period. (refer to Figure 3-2).

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- A safety follow-up period up to 12 weeks with 3 outpatient visits on Days 113, 127 and 155

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- An end of study visit scheduled on Day183

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The renal biopsy to be collected during run-in is mandatory in case the most recent bioptic material is older than 3 months. The renal biopsy to be collected at Week 12 is mandatory.

Patients will remain on their supportive therapy, i.e. ACEi and/or ARB or other antihypertensive therapy, Commercially Confidential Information for the duration of the trial. To be dosed patients must have been on stable therapy with an ACEi and/or ARB.

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During the treatment period, no change in medication is allowed except for safety reasons.

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Patients must receive vaccinations against *N. meningitidis*, *S. pneumoniae* and *H. influenzae* prior to first LNP023 dosing.

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Efficacy in terms of reversal of histopathologic changes will be assessed after the 12-week treatment period. Proteinuria and individual clinical response to various pharmacodynamic markers as well as pharmacokinetics will be assessed over the 12-week treatment period (refer to Table 8-3 and Table 8-4 for detailed sampling time).

In this context, proteinuria will be assessed by collecting 24-h urine and first morning void urine to assess the change in and evolution of: UA and UP excretion, UACR and UPCR, creatinine clearance and hematuria.

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Safety monitoring includes the following assessments for each visit during Treatment periods and alerts will be set up for abnormal values to be reported immediately to investigator and sponsor:

- Renal function surveillance including serum creatinine, eGFR (using the CKD-EPI formula), hematuria, 24-h UA, UACR and UPCR assessments (refer to Section 8.3)
- Blood pressure (refer to Section 8.4.4.2)
- Commercially Confidential Information
- 12-lead ECG (refer to Section 8.4.2)
- Infection surveillance (refer to Section 10.2.3)
- Liver safety (refer to Section 10.2.1)
- Hematology and blood chemistry parameters (refer to Section 8.4.1)
- Vital signs (refer to Section 8.4.4)
- Physical examination (refer to Section 8.4.7)

- AEs and SAEs recording (refer to Section 10)

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4 Rationale

4.1 Rationale for study design

The study has two separate cohorts (A and B), since two distinct C3G patient populations are investigated.

In both Cohorts the study treatment period starts with a within-patient dose-escalation portion of 4 weeks, to establish a Dose-PD and PK-PD relationship for LNP023 and to assess the relationship between LNP023 PD-effect and efficacy. To this end patients will be treated with increasing doses of LNP023,

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A PK assessment will be done on the last day of the respective dose level. The key biomarkers that will be assessed in this study are C3, and Bb as they have been shown to be dysregulated in patients with C3G (Nester and Smith 2016; Zhang et al 2014). Other biomarkers may be investigated.

Treatment period following the dose-escalation portion, includes a CCI period for both Cohorts. In Cohort A, this will be used to assess the primary objective of efficacy with LNP023 (200 mg dose CCI), i.e., to reduce proteinuria in the specific C3G non-transplanted population. This endpoint was chosen since urinary protein levels are known to correlate with kidney function/inflammation and therefore are expected to provide an objective means to measure drug effect. Importantly, Cohort B will also assess histopathologic improvement in renal biopsies. Biopsy response will be investigated in transplanted patients, due to higher availability of preexisting baseline biopsies (biopsies taken within 3 months before the baseline visit) and the higher acceptance of kidney biopsies at the end of treatment in this particular population.

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The underlying pathophysiology causing C3G is uncontrolled activation of the AP of the complement system (Medjeral-Thomas et al 2014) manifesting as two major subgroups that are recognized based on electron microscopic appearance as either C3 glomerulonephritis, or dense deposit disease (Sethi et al 2017). Treatment options for these disorders are quite limited, and disease progression often leads to end-stage renal disease requiring renal replacement therapy and/or kidney transplantation. To note, both diagnoses recur in most patients after transplantation, leading to graft loss in up to half of affected cases. In the largest reported series to date with C3GN who underwent renal transplantation from the Mayo Clinic, 68% developed recurrent C3GN. The median time to recurrence was 28 months but starting as early as 9 days post transplant, highlighting the high unmet medical need especially for this population receiving an allograft for C3G related end-stage renal disease (Braun et al 2005;

Zand et al 2014). In order to create evidence that Factor B inhibition ameliorates C3G in both, native- as well as transplanted kidneys, Cohort A and B will be conducted concurrently. Trial experience with LNP023 to date indicate that treatment with LNP023 was well tolerated; as single agent treatment (ongoing study CLNP023X2203 in IgA nephropathy), or as add-on therapy for PNH patients with active hemolysis despite C5 complement inhibition with eculizumab (CLNP023X2201, ongoing). Studies with other complement inhibitors such as eculizumab further support the safety of the proposed approach demonstrating that broader complement inhibition (anti C5) also in immunosuppressed patients post kidney transplantation was well tolerated (e.g., studies Stegall et al 2011; Bentall et al 2014; NCT00670774; NCT01399593; NCT01567085; NCT02145182 in CT.gov website).

Since the intrinsic turnover rate of C3 and Bb is known to be in the range of a few minutes to hours (Kirschfink and Mollnes 2003), near complete steady state conditions are likely to be achieved within 1 week of starting each new dose level. Thus measurements of PD effect at the end of each one week dosing period are considered to provide reliable data for assessment of PK/PD relationship.

In aggregate, concomitant determination of PK, PD, and Dose-PD relation at different dose levels is intended to provide data to support dose selection for subsequent confirmatory studies. A conventional dose-ranging study with different doses in separate treatment arms was not pursued due to the low prevalence of the disease.

In order to establish a Dose/PD relationship based on complement biomarkers, only C3G patients with reduced C3 levels at baseline will be included into Cohort A.

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However due to higher acceptance of kidney biopsies in this population we will seek to demonstrate histologic improvement in this patient population in addition to improvement in UP and UA. Histologic evaluation of kidney biopsies will focus on the pillars: C3 deposits, disease activity in C3G lesions and chronic C3G related changes in the kidney. Each of these pillars will be evaluated by scores that comprise different light-, fluorescence- and electron-microscopical parameters. Collectively these parameters will allow to determine if blockade of Factor B is sufficient to reduce C3 deposition and disease activity. Reversal of chronic changes is not expected within the timeframe of the proposed study.

Three different types of urine collection will be used: first morning void urine collection, 24-h urine collection, and spot midstream urine collection. The first method will be used for inclusion criteria assessment and easy monitoring, the second will be used during baseline and treatment to evaluate the creatinine clearance, the third will be used for biomarker analysis, and safety monitoring.

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Patients in both Cohorts will be offered the possibility to roll-over directly in an extension study at the end of Treatment period Commercially Confidential Information

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4.1.1 Rationale for choice of background therapy

LNP023 blocks FB and thereby the AP, which is important for the defense against microbes. Thus, patients with mutations of FB are generally healthy, but have impaired resistance against selected 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*. With the vaccination described above, the risk for serious infection during LNP023 treatment is considered to be very low. Relevant vaccinations should be performed prior to initiation of LNP023. Commercially Confidential Information

. Further details and the vaccination strategy are outlined in Section 8.4.9.

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4.2 Rationale for dose/regimen and duration of treatment

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

Not applicable.

4.4 Purpose and timing of interim analyses/design adaptations

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4.5 Risks and benefits

LNP023 has not been previously administered with therapeutic intent to patients with C3G. Therefore, no statement can be made at this time on the actual clinical benefits of LNP023 in this patient population. However, given the mechanism of action of LNP023 targeting the complement system as discussed in the background (Section 1.1), there is good rationale to believe that a therapeutic response can be achieved with the compound in patients with C3G.

Assuming a positive benefit-risk assessment (i.e., a clinically meaningful reduction in urinary protein excretion, and/or improvement in histology) it has been agreed with Health Authorities to offer CLNP023X2202 patients roll-over into the extension study CLNP023B12001B if the Investigator deems it to be clinically beneficial for the patient.

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The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring during the study and stopping rules. Guidance for the investigators is included in the IB.

Women of child bearing 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 outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

There may be unknown risks of LNP023 which may be serious.

4.5.1 Blood sample volume

If patient will complete only Treatment period : approximately 670 mL of blood is planned to be collected during Screening period, Treatment period and the follow-up period (i.e., over a period up to about 38 weeks from each subject from screening until EOS) from both Cohorts.

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Additional samples may be required for safety monitoring.

The timing of blood sample collections is outlined in the Assessment schedule (refer to Section 8).

A summary blood log is provided in the Site Operations Manual. Instructions for all sample collection, processing, storage and shipment information are also available in the SOM and Central Laboratory Manual.

Refer to Section 8.5.3.6 regarding the potential use of residual samples.

4.5.2 Potential risks

The potential risk of LNP023 can only be assessed indirectly by analyzing the pharmacological profile, preclinical safety studies and clinical studies.

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4.5.3 Risk for infections

In this study, LNP023 is used to block the complement AP. Patients with mutations of factor B are generally perfectly healthy, but have impaired resistance against bacterial infections. Of particular concern are rare, but serious, meningococcal or pneumococcal infections. In the general population the annual incidence of invasive infections with *Neisseria meningitidis* is between 0.1-2.0 cases per 100,000 with great variation between regions (Sridhar et al 2015). For infections with *Streptococcus pneumoniae*, the annual risk is 35 cases per 100,000 for individuals <2 or >65 years of age, while it is 4 cases per 100,000 in individuals between 18 and 35 years of age (Alanee et al 2007). The current risk for invasive infections with *Hemophilus influenzae* is 1.6 per 100,000 in the US (MacNeil et al 2011).

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Vaccination is predicted to be an effective mitigation strategy to reduce the risk for individuals treated with LNP023.

After a single injection of meningococcal vaccine, high titers are achieved after two weeks, but in most studies data on titers at Day 28 are reported (Gossger et al 2012, Keyserling et al 2005). Similar effects are seen with the pneumococcal vaccines McFetridge et al 2015, Bryant et al 2015). Vaccinations should be performed prior to initiation of LNP023.
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During the two-month Screening period, vaccination will be done according to local regulation and practice prior to treatment to effectively increase the serological titers and reduce the risk for the individual in the unlikely event of bacterial infection with *N. meningitidis*, *S. pneumoniae* or *H. influenzae*. The vaccines and the vaccination procedures recommended vary between countries.

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Patients must receive vaccinations against *N. meningitidis*, *S. pneumoniae* and *H. influenzae* prior to first LNP023 dosing.

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4.5.4 Risk for testis tubular degeneration

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Notably, no obvious fertility issue was observed in the complement FB knockout mouse model (Matsumoto 1999) or patients with genetic mutations in the complement AP (Skattum et al 2011).

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4.5.6 Non-clinical safety findings of undetermined relevance

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4.5.7 Risk mitigation strategy

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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 8-1and Table 8-3). In addition to standard clinical laboratory assessments, subjects will be monitored regularly for signs and symptoms of infections, inflammation, and hematologic and renal function as outlined below. Patients 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.

In agreement with the primary and secondary objectives, measurement of UPCR and UACR, 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.

Finally, key safety data will be reviewed by the Sponsor on an ongoing basis.

5 Population

As direct renal clearance has been shown to be a significant but not a predominant clearance pathway, this trial may enroll patients with mild-to-moderate renal impairment.

5.1 Inclusion criteria

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

Population for Cohort A

Approximately 15 C3G patients with native kidneys and with reduced serum C3 levels (male or female) will be enrolled in Cohort A to ensure that 12 patients complete the study in this cohort.

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female patients 18 years old or older at screening visit
3. Patients must have C3G as confirmed by renal biopsy within twelve months prior to enrollment (confirmation by the Investigator is required).
4. C3G patients with reduced C3 at screening Commercially Confidential Information
5. Able to communicate well with the investigator, to understand and comply with the requirements of the study.
6. At screening and baseline visits, patients must weigh at least 35 kg to participate in the study, Commercially Confidential Information
7. Vital signs should be within the following ranges :
   body temperature between 35.0-37.5 °C systolic blood pressure, 80-170 mm Hg diastolic blood pressure, 50-105 mm Hg pulse rate, 45 - 100 bpm
8. Estimated GFR (using the CKD-EPI formula) ≥30 mL/min per 1.73 m^2 for patients on a maximum recommended or maximum tolerated dose of an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB).
9. UPCR ≥ 100 mg/mmol sampled from first morning void (or ≥ 1 g/24h total urinary protein excretion from a 24h collection during run-in) at run-in (Visit 20) or at baseline (Visit 30).
11. Prior to Day 1, all patients must have been on supportive care including a maximally tolerated dose of ACEi or ARB for at least 30 days.

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12. Commercially Confidential Information

14. Commercially Confidential Information

15 Commercially Confidential Information

Population for Cohort B

Approximately 12 C3G kidney transplanted patients (male or female) with C3G recurrence will be enrolled in Cohort B to ensure that at least 10 complete the study in this cohort.

16. Written informed consent must be obtained before any assessment is performed.
17. Male and female patients 18 years old or older at screening visit
18. Patients must have C3G recurrence after transplantation as confirmed by renal biopsy after transplantation within twelve months prior to enrollment (confirmation by the Investigator is required).
19. Able to communicate well with the investigator, to understand and comply with the requirements of the study.
20. At screening and baseline visits, patients must weigh at least 35 kg to participate in the study, Commercially Confidential Information

21. Vital signs should be within the following ranges:
    body temperature between 35.0-37.5 °C systolic blood pressure, 80-170 mm Hg diastolic blood pressure, 50-105 mm Hg pulse rate, 45 - 100 bpm
22. Commercially Confidential Information
23. Normal or elevated urinary protein excretion at screening or at baseline (Visit 30).
25. Commercially Confidential Information

26. Commercially Confidential Information

27. No histological/laboratory/clinical signs of allorejection
28. If applicable, induction treatment after allotransplantation needs to be completed >30 days before screening visit.
29. Transplantation of a kidney allograft >90 days before screening visit
30. Patients need to be on a stable dose of immunsuppressive regimen CCI
    prior to Day 1. Any approved treatments are allowed for this purpose (if not prohibited as per protocol).
32. Commercially Confidential Information

33. Commercially Confidential Information

5.2 Exclusion criteria

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

Population for Cohort A

Approximately 15 C3G patients with native kidneys and with reduced serum C3 levels (male or female) will be enrolled in Cohort A to ensure that 12 patients complete the study in this cohort.

1. Commercially Confidential Information
2. Use of other investigational drugs at the time of enrollment, or within 5 half-lives, or within 30 days of screening, whichever is longer; or longer if required by local regulations
3. A history of clinically significant ECG abnormalities,

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4. Known family history or known presence of long QT syndrome or Torsades de Pointes
5. Use of agents known to prolong the QT interval unless they can be permanently discontinued for the duration of the study
6. Commercially Confidential Information

7. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
8. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 1 week after stopping of investigational drug.

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12. History of immunodeficiency diseases, or a positive HIV test result at screening visit.
13. Commercially Confidential Information
14. Chronic infection with Hepatitis B (HBV) or Hepatitis C (HCV) at screening visit.
15. Commercially Confidential Information

16. Patients who cannot receive vaccinations against *N. meningitidis*, *S. pneumoniae*, or *H. influenzae*.
17. Commercially Confidential Information

18. Commercially Confidential Information

19. Commercially Confidential Information

42. Commercially Confidential Information

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects

Population for Cohort B

Approximately 12 C3G kidney transplanted patients (male or female) with C3G recurrence will be enrolled in Cohort B to ensure that at least 10 complete the study in this cohort.

20. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 30 days, whichever is longer; or longer if required by local regulations.
21. A history of clinically significant ECG abnormalities,

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22. Known family history or known presence of long QT syndrome or Torsades de Pointes
23. Use of agents known to prolong the QT interval unless they can be permanently discontinued for the duration of the study
24. Commercially Confidential Information

25. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.

26. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 1 week after stopping of investigational drug.

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30. History of immunodeficiency diseases, or a positive HIV test result at screening visit.
31. Commercially Confidential Information
32. Chronic infection with Hepatitis B (HBV) or Hepatitis C (HCV) at screening visit
33. Commercially Confidential Information

34. Patients who cannot receive vaccinations against *N. meningitidis*, *S. pneumoniae*, or *H. influenzae*
35. Commercially Confidential Information

36. Commercially Confidential Information
37. Commercially Confidential Information

38. Commercially Confidential Information
39. Commercially Confidential Information

40. Commercially Confidential Information

41. Commercially Confidential Information

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects

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 Site Operations Manual (SOM).

6.1.1 Investigational and control drugs

The investigational drug, LNP023 as 5 mg, 25 mg, 100 mg capsules will be prepared by Novartis and supplied to investigator sites as open label subject packs.

Table 6-1 Overview of study medication

Investigational Drug	Pharmaceutical Dosage Form	Route of Administration	Packaging	Sponsor
LNP023 5 mg	Capsules	Oral use	Open label subject packs; bottles	Sponsor global
LNP023 25 mg	Capsules	Oral use	Open label subject packs; bottles	Sponsor global
LNP023 100 mg	Capsules	Oral use	Open label subject packs; bottles	Sponsor global

6.1.1.1 Bio-batch retention samples

Not applicable for this study.

6.1.2 Additional study treatments

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

6.1.3 Treatment arms/group

This is an open label study where approximately 15 patients enrolled into Cohort A and approximately 12 patients into Cohort B will be treated for up to 14 weeks CCI with LNP023 CCI :

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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 the subject was enrolled into the study.

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 in the specific CRF page.

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Patients must receive vaccinations against *N. meningitidis*, *S. pneumoniae* and *H. influenzae* prior to first LNP023 dosing.

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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 enrolling a patient or allowing a new medication to be started. If the patient is already enrolled, contact the Sponsor to determine if the patient should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

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list of drug to be used with caution will be provided to the Investigators.

6.2.2 Prohibited medication

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Use of the treatments displayed in the table below is NOT allowed in patients enrolled in Cohort A and Cohort B.

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6.2.3 Rescue medication

Not applicable.

6.2.4 Restriction for study subjects

There are no specific restrictions

6.2.4.1 Dietary restrictions and smoking

There are no specific dietary or smoking restrictions.

6.2.4.2 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 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

This is an open label study, no randomization to be performed.

6.4 Treatment blinding

Treatment will be open to subjects, investigator staff, persons performing the assessments, and the CTT.

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments and/or interruptions are not permitted during Treatment period

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6.6 Additional treatment guidance

6.6.1 Treatment compliance

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

The investigator must promote compliance by instructing the subject to take the study treatment 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 will be assessed by the Investigator and/or study personnel at each visit using pill counts and information provided by the subject in the diaries. 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.

6.6.2 Recommended treatment of adverse events

At present, there is insufficient information to provide specific recommendations regarding treatment of AEs. There is no treatment that can reverse the activity of LNP023. LNP023 is a small molecule with a half-life of 12 hours. Potential AEs should therefore be treated symptomatically at the discretion of the Investigator. Medication used to treat AEs must be recorded on the specific CRF page.

6.6.3 Emergency breaking of assigned treatment code

Not applicable since this is an open label study.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under the investigational and control drugs section (refer to Section 6.1.1).

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

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See the SOM for further details.

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.

Sponsor 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 by Sponsor before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the IB. 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 between IB updates 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 child bearing 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.

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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 lists all of the assessments and indicates with an "X", the visits 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 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.

Table 8-1 Assessment Schedule, Cohort A

						Treatment Period														
Period	**Screening**					CCI				CCI			CCI			CCI				
Visit Name	**Screening**	**Run-in**		**Baseline**																
Visit Numbers[1]	**1**	**20**		**30**	**40**	**100**	**110**			**120**			**130**			**140**	**150**	**160**	**170**	**180**
Days	**-90 to -30**	**-89 to -40**	**-60 to -30**	**-30**	**-1**	**1**	**7**			**14**			**21**			**28**	**29**	**36**	**64**	**84**
Time (post-dose)	**-**	**-**	**-**	**-**	**-**	**Pre-dose**	**Pre-dose**	**0.5h**	**8h**	**Pre-dose**	**0.5h**	**8h**	**Pre-dose**	**0.5h**	**8h**	**Pre-dose**	**-**	**-**	**-**	**-**
Informed consent	X																			
CCI																				
Demography	X																			
Inclusion / Exclusion criteria	X			X	X[3]															
Medical history/current medical conditions	X			X	X															
Prior medications	X																			
Physical Examination	S				S															S
Hepatitis and HIV screen	S																			
Tuberculosis status	X																			
Pregnancy and assessments of fertility[4]	S				S											S			S	S
CCI				X[5]														X[6]		X[6]
Renal biopsy		X[7,8]																		X[2]
CCI	S			S																
CCI	X																			
CCI	X				X											X				X

						Treatment Period															
Period	**Screening**					CCI															
Visit Name	**Screening**	**Run-in**		**Baseline**																	
Visit Numbers[1]	**1**	**20**		**30**	**40**	**100**	**110**			**120**			**130**			**140**	**150**	**160**	**170**	**180**	
Days	**-90 to -30**	**-89 to -40**	**-60 to -30**	**-30**	**-1**	**1**	**7**			**14**			**21**			**28**	**29**	**36**	**64**	**84**	
Time (post-dose)	**-**	**-**	**-**	**-**	**-**	**Pre-dose**	**Pre-dose**	**0.5h**	**8h**	**Pre-dose**	**0.5h**	**8h**	**Pre-dose**	**0.5h**	**8h**	**Pre-dose**	**-**	**-**	**-**	**-**	
Vital Signs[7,9,11]	See table below																				
ECG evaluation[10]	X			X	X	X[28]	X			X			X			X		X[28]	X	X	
Hematology[7,11]	X			X		X	X			X			X			X		X	X	X	
Blood chemistry[7,11,12]	X			X		X	X			X			X			X		X	X	X	
Urinalysis[7,11]	X			X		X	X			X			X			X		X	X	X	
Vaccination[13,14]		X	X[15]																		
Study drug dispensation						X			X[27]			X[27]			X[27]			X	X		
24-hours urine collection[16]		X[31]				X										X				X	
Spot urine collection - First Morning Void[7]		X[17]		X[17]			X[17]			X[17]			X[17]					X[17]	X[17]		
Spot urine collection - Mid Stream[18,19]						X		X			X			X			X	X	X	X	
CCI	X			X		X	X			X			X			X		X	X	X	
eGFR	X			X		X	X			X			X			X		X	X	X	
PK sample collection	See table below																				
C3	See table below																				
Complement pathway biomarkers in plasma[21]	See table below																				
CCI CCI						CCI															

						Treatment Period															
Period	**Screening**					CCI				CCI			CCI			CCI				
Visit Name	**Screening**	**Run-in**		**Baseline**																	
Visit Numbers[1]	**1**	**20**		**30**	**40**	**100**	**110**			**120**			**130**			**140**	**150**	**160**	**170**	**180**
Days	**-90 to -30**	**-89 to -40**	**-60 to -30**	**-30**	**-1**	**1**	**7**			**14**			**21**			**28**	**29**	**36**	**64**	**84**
Time (post-dose)	**-**	**-**	**-**	**-**	**-**	**Pre-dose**	**Pre-dose**	**0.5h**	**8h**	**Pre-dose**	**0.5h**	**8h**	**Pre-dose**	**0.5h**	**8h**	**Pre-dose**	**-**	**-**	**-**	**-**
Complement pathway biomarkers in serum[23]	See table below																				
CCI				X		X	X			X			X			X			X	X
Subject domiciled						X										X				X
Subject discharged						X											X			
Adverse Events / Serious Adverse Events[24]	X																				
Concomitant medications / therapies	X																				
CCI						X															
Study completion information																					
Safety Follow up Call																					

		Treatment Period	Safety Follow-up period						
Period			CCI						
Visit Name	CCI		CCI		**Follow-up**			**EOS**	**Post study safety contact**
Visit Numbers[1]	**190**	**195**	**200**	**210**	**230**	**240**	**250**	**1999**	
Days	**85**	**169**	**92 or 176**	**99 or 183**	**113 or 197**	**127 or 211**	**155 or 239**	**183 or 267**	**Last treatment + 30 days**
Time (post-dose)	**-**	**-**		**-**	**-**	**-**	**-**	**-**	**-**
Informed consent									
CCI									
Demography									
Inclusion / Exclusion criteria									
Medical history/current medical conditions									
Prior medications									
Physical Examination		S						S	
Hepatitis and HIV screen									

		Treatment Period	Safety Follow-up period						
Period			CCI						
Visit Name	CCI		CCI		Follow-up			EOS	Post study safety contact
Visit Numbers[1]	**190**	**195**	**200**	**210**	**230**	**240**	**250**	**1999**	
Days	**85**	**169**	**92 or 176**	**99 or 183**	**113 or 197**	**127 or 211**	**155 or 239**	**183 or 267**	**Last treatment + 30 days**
Time (post-dose)	**-**	**-**		**-**	**-**	**-**	**-**	**-**	**-**
Tuberculosis status									
Pregnancy and assessments of fertility[4]		S		S				S	
CCI									
Renal biopsy									
CCI									
CCI									
CCI		X							
Vital Signs[7,9,11]	See table below								
ECG evaluation[10]		X		X	X		X	X	
Hematology[7,11]		X		X	X	X	X	X	
Blood chemistry[7,11,12]		X		X	X	X	X	X	

		Treatment Period	Safety Follow-up period						
Period			CCI						
Visit Name	CCI		CCI		**Follow-up**			**EOS**	**Post study safety contact**
Visit Numbers[1]	**190**	**195**	**200**	**210**	**230**	**240**	**250**	**1999**	
Days	**85**	**169**	**92 or 176**	**99 or 183**	**113 or 197**	**127 or 211**	**155 or 239**	**183 or 267**	**Last treatment + 30 days**
Time (post-dose)	**-**	**-**		**-**	**-**	**-**	**-**	**-**	**-**
Urinalysis[7,11]		X		X	X	X	X	X	
Vaccination[13,14]									
Study drug dispensation	X[30]	X[27]	X[27]						
24-hours urine collection[16]	X								
Spot urine collection - First Morning Void[7]		X[17]	X[17]	X[17]	X[17]	X[17]	X[17]	X[17]	
Spot urine collection - Mid Stream[18,19]		X	X	X	X			X	
CCI		X		X	X	X	X	X	
eGFR		X	X	X	X	X		X	
PK sample collection	See table below								
C3	See table below								

		Treatment Period	Safety Follow-up period						
Period			CCI						
Visit Name	CCI		CCI		Follow-up			EOS	Post study safety contact
Visit Numbers[1]	**190**	**195**	**200**	**210**	**230**	**240**	**250**	**1999**	
Days	**85**	**169**	**92 or 176**	**99 or 183**	**113 or 197**	**127 or 211**	**155 or 239**	**183 or 267**	**Last treatment + 30 days**
Time (post-dose)	**-**	**-**		**-**	**-**	**-**	**-**	**-**	**-**
Complement pathway biomarkers in plasma[21]	See table below								
CCI									
Complement pathway biomarkers in serum[23]	See table below								
CCI		X						X	
Subject domiciled	X								
Subject discharged	X								

		Treatment Period	Safety Follow-up period						
Period			CCI						
Visit Name	CCI		CCI		**Follow-up**			**EOS**	**Post study safety contact**
Visit Numbers[1]	**190**	**195**	**200**	**210**	**230**	**240**	**250**	**1999**	
Days	**85**	**169**	**92 or 176**	**99 or 183**	**113 or 197**	**127 or 211**	**155 or 239**	**183 or 267**	**Last treatment + 30 days**
Time (post-dose)	**-**	**-**		**-**	**-**	**-**	**-**	**-**	**-**
Adverse Events / Serious Adverse Events[24]	X								
Concomitant medications / therapies	X								
CCI	X								
Study completion information								X	
Safety Follow up Call									S

[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] Visit structure given for internal programming purpose only
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[3] Verify again the Inclusion Criteria #5,6,7, 11,12 and the Exclusion Criteria # 3, 5, 7, 8, 9, 10.
[4] Serum pregnancy test required at screening and at end of treatment. Urine pregnancy test at further time points.
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[7] During treatment, assessment is performed pre morning dose
[8] Renal biopsy has to be performed any time during screening period in case the most recent bioptic material is older than 12 months.
[9] Includes pulse rate, blood pressure and temperature
[10] Triplicate ECGs at all visits
[11] Including infection surveillance
[12] Including liver safety monitoring (ALT, AST, ALP, TBL, PT/INR, γGT levels assessment)
[13] If not previously vaccinated, patients will receive vaccination against *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* according to local guidelines
Commercially Confidential Information
[16] Includes UACR and UPCR, 24h urine excretion of albumin and protein, (PK only at Visit 140)
Commercially Confidential Information
[19] During treatment, collection should be performed possibly at the same time, i.e. about half an hour after morning dose at site, except at Visit 180, where collection should be performed before starting the 24h urine collection, independently by the dose intake.
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[21] Including, but not limited to, Factor Bb, and sC5b-9
Commercially Confidential Information
[24] All AEs will be collected from Informed Consent until the End Of Study visit, all SAEs will be collected until 30 days after the End Of Study visit
Commercially Confidential Information
[27] New dose capsules to be dispensed, see SOM for details
[28] To be performed pre-dose and 1h post dose
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[31] It may be performed for screening purposes.

Table 8-2 Details for highly repetitive assessments, Cohort A

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Table 8-3 Assessment Schedule, Cohort B

						Treatment period														
Period	**Screening**					CCI				CCI			CCI			CCI				
Visit Name	**Screening**	**Run-in**		**Baseline**																
Visit Numbers[1]	**1**	**20**		**30**	**40**	**100**	**110**			**120**			**130**			**140**	**150**	**160**	**170**	**180**
Days	**-90 to -30**	**-89 to -40**	**-60 to -30**	**-30**	**-1**	**1**	**7**			**14**			**21**			**28**	**29**	**36**	**64**	**84**
Time (post-dose)	**-**	**-**	**-**	**-**	**-**	**Pre-dose**	**Pre-dose**	**0.5h**	**8h**	**Pre-dose**	**0.5h**	**8h**	**Pre-dose**	**0.5h**	**8h**	**Pre-dose**	**-**	**-**	**-**	**-**
Informed consent	X																			
CCI	X																			
Demography	X																			
Inclusion / Exclusion criteria	X			X	X[3]															
Medical history/current medical conditions	X			X	X															
Prior medications	X																			
Physical Examination	S				S															S
Hepatitis and HIV screen	S																			
Tuberculosis status	X																			
Pregnancy and assessments of fertility[4]	S				S											S			S	S
CCI				X[5]														X[6]		X[6]
Renal biopsy		X[7]																		X
CCI	S			S																
CCI	X																			
CCI	X				X											X				X
Vital Signs[8,9,11]	See table below																			

						Treatment period														
Period	**Screening**					CCI				CCI			CCI			CCI				
Visit Name	**Screening**	**Run-in**		**Baseline**																
Visit Numbers[1]	**1**	**20**		**30**	**40**	**100**	**110**			**120**			**130**			**140**	**150**	**160**	**170**	**180**
Days	**-90 to -30**	**-89 to -40**	**-60 to -30**	**-30**	**-1**	**1**	**7**			**14**			**21**			**28**	**29**	**36**	**64**	**84**
Time (post-dose)	**-**	**-**	**-**	**-**	**-**	**Pre-dose**	**Pre-dose**	**0.5h**	**8h**	**Pre-dose**	**0.5h**	**8h**	**Pre-dose**	**0.5h**	**8h**	**Pre-dose**	**-**	**-**	**-**	**-**
ECG evaluation[10]	X			X	X	X[29]	X			X			X			X		X[29]	X	X
Hematology[8,11]	X			X		X	X			X			X			X		X	X	X
Blood chemistry[8,11,12]	X			X		X	X			X			X			X		X	X	X
Urinalysis[8,11]	X			X		X	X			X			X			X		X	X	X
Vaccination[13,14]		X	X[15]																	
Study drug dispensation						X			X[28]			X[28]			X[28]			X	X	
24-hours urine collection[16]		X[32]				X										X[17]				X[17]
Spot urine collection - First Morning Void[8]		X[18]		X[18]			X[18]			X[18]			X[18]					X[18]	X[18]	
Spot urine collection - Mid Stream[19,20]						X[17]		X			X			X			X[17]	X[17]	X[17]	X[17]
CCI	X			X		X	X			X			X			X		X	X	X
eGFR	X			X		X	X			X			X			X		X	X	X
PK sample collection	See table below																			
C3	See table below																			
Complement pathway biomarkers in plasma[22]	See table below																			
Complement pathway biomarkers in serum[23]	See table below																			

						Treatment period														
Period	**Screening**					CCI				CCI			CCI			CCI				
Visit Name	**Screening**	**Run-in**		**Baseline**																
Visit Numbers[1]	**1**	**20**		**30**	**40**	**100**	**110**			**120**			**130**			**140**	**150**	**160**	**170**	**180**
Days	**-90 to -30**	**-89 to -40**	**-60 to -30**	**-30**	**-1**	**1**	**7**			**14**			**21**			**28**	**29**	**36**	**64**	**84**
Time (post-dose)	**-**	**-**	**-**	**-**	**-**	**Pre-dose**	**Pre-dose**	**0.5h**	**8h**	**Pre-dose**	**0.5h**	**8h**	**Pre-dose**	**0.5h**	**8h**	**Pre-dose**	**-**	**-**	**-**	**-**
CCI						CCI														
CCI				X		X	X			X			X			X			X	X
Subjects domiciled						X										X				X
Subject discharged						X											X			
CCI						X														
Adverse Events / Serious Adverse Events[27]	X																			
Concomitant medications / therapies	X																			
Study completion information																				
Safety Follow up Call																				

		Treatment Period	Safety Follow-up period						
Period			**Dosing tapering period**		**Safety follow-up**				**-**
Visit Name	CCI		CCI		**Follow-up**			**EOS**	**Post study safety contact**
Visit Numbers[1]	**190**	**195**	**200**	**210**	**230**	**240**	**250**	**1999**	
Days	**85**	**169**	**92 or 176**	**99 or 183**	**113 or 197**	**127 or 211**	**155 or 239**	**183 or 267**	**Last treatment + 30 days**
Time (post-dose)	**-**		**-**	**-**		**-**	**-**	**-**	**-**
Informed consent									
CCI									
Demography									
Inclusion / Exclusion criteria									
Medical history/current medical conditions									
Prior medications									
Physical Examination		S						S	
Hepatitis and HIV screen									

		Treatment Period	Safety Follow-up period						
Period			**Dosing tapering period**		**Safety follow-up**				**-**
Visit Name	CCI		CCI		**Follow-up**			**EOS**	**Post study safety contact**
Visit Numbers[1]	**190**	**195**	**200**	**210**	**230**	**240**	**250**	**1999**	
Days	**85**	**169**	**92 or 176**	**99 or 183**	**113 or 197**	**127 or 211**	**155 or 239**	**183 or 267**	**Last treatment + 30 days**
Time (post-dose)	**-**		**-**	**-**		**-**	**-**	**-**	**-**
Tuberculosis status									
Pregnancy and assessments of fertility[4]		S		S				S	
CCI									
Renal biopsy									
CCI									
CCI									
CCI		X							
Vital Signs[8,9,11]	See table below								
ECG evaluation[8,10]		X		X	X		X	X	

		Treatment Period	Safety Follow-up period						
Period			**Dosing tapering period**		**Safety follow-up**				**-**
Visit Name	CCI		CCI		**Follow-up**			**EOS**	**Post study safety contact**
Visit Numbers[1]	**190**	**195**	**200**	**210**	**230**	**240**	**250**	**1999**	
Days	**85**	**169**	**92 or 176**	**99 or 183**	**113 or 197**	**127 or 211**	**155 or 239**	**183 or 267**	**Last treatment + 30 days**
Time (post-dose)	**-**		**-**	**-**		**-**	**-**	**-**	**-**
Hematology[8,11]		X		X	X	X	X	X	
Blood chemistry[8,11,12]		X		X	X	X	X	X	
Urinalysis[8,11]		X		X	X	X	X	X	
Vaccination[13,14]									
Study drug dispensation	X[31]	X[28]	X [28]						
24-hours urine collection[16]	X[17]								
Spot urine collection - First Morning Void[8]		X	X[18]	X[18]	X[18]	X[18]	X[18]	X[18]	
Spot urine collection - Mid Stream[19,20]		X	X[17]	X[17]	X[17]			X[17]	
CCI		X		X	X	X	X	X	

		Treatment Period	Safety Follow-up period						
Period			**Dosing tapering period**		**Safety follow-up**				**-**
Visit Name	CCI		CCI		**Follow-up**			**EOS**	**Post study safety contact**
Visit Numbers[1]	**190**	**195**	**200**	**210**	**230**	**240**	**250**	**1999**	
Days	**85**	**169**	**92 or 176**	**99 or 183**	**113 or 197**	**127 or 211**	**155 or 239**	**183 or 267**	**Last treatment + 30 days**
Time (post-dose)	**-**		**-**	**-**		**-**	**-**	**-**	**-**
eGFR		X	X	X	X	X		X	
PK sample collection	See table below								
C3	See table below								
Complement pathway biomarkers in plasma[22]	See table below								
Complement pathway biomarkers in serum[23]	See table below								
CCI									
CCI		X						X	
Subjects domiciled	X								

		Treatment Period	Safety Follow-up period						
Period			**Dosing tapering period**		**Safety follow-up**				**-**
Visit Name	CCI		CCI		**Follow-up**			**EOS**	**Post study safety contact**
Visit Numbers[1]	**190**	**195**	**200**	**210**	**230**	**240**	**250**	**1999**	
Days	**85**	**169**	**92 or 176**	**99 or 183**	**113 or 197**	**127 or 211**	**155 or 239**	**183 or 267**	**Last treatment + 30 days**
Time (post-dose)	**-**		**-**	**-**		**-**	**-**	**-**	**-**
Subject discharged	X								
CCI	X								
Adverse Events / Serious Adverse Events[27]	X								
Concomitant medications / therapies	X								
Study completion information								X	
Safety Follow up Call									S

[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] Visit structure given for internal programming purpose only
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[3] Verify again Inclusion Criteria # 19, 20, 21, 25, 26 and Exclusion Criteria # 21, 23, 25, 26, 27, 28.
[4] Serum pregnancy test required at screening and at end of treatment. Urine pregnancy test at further time points.
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[7] Renal biopsy has to be performed any time during the screening period, in case the most recent bioptic material is older than 3 months.
[8] During treatment period, the assessment is performed pre morning dose
[9] Includes pulse rate, blood pressure and temperature
[10] Triplicate ECGs at all visits
[11] Including infection surveillance
[12] Including liver safety monitoring (ALT, AST, ALP, TBL, PT/INR, γGT levels assessment)
[13] If not previously vaccinated, patients will receive vaccination against Neisseria meningitidis, Streptococcus pneumoniae, and Haemophilus influenzae according to local guidelines
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[16] Includes UACR and UPCR, 24h urine excretion of albumin and protein, (PK only at Visit 140)
[17] To be performed at site
Commercially Confidential Information

[20] During treatment, collection should be performed possibly at the same time, i.e. about half an hour after morning dose at site, except at Visit 180 where collection should be performed before starting 24h urine collection, independently by the dose intake
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[27] All AEs will be collected from Informed Consent until the End Of Study visit, all SAEs will be collected until 30 days after the End Of Study visit
[28] New dose capsules to be dispensed, see SOM for details
[29] To be performed pre-dose and 1h post dose
Commercially Confidential Information

[32] It may be performed for screening purposes

		Treatment Period	Safety Follow-up period						
Period			**Dosing tapering period**		**Safety follow-up**				**-**
Visit Name	CCI		CCI		**Follow-up**			**EOS**	**Post study safety contact**
Visit Numbers[1]	**190**	**195**	**200**	**210**	**230**	**240**	**250**	**1999**	
Days	**85**	**169**	**92 or 176**	**99 or 183**	**113 or 197**	**127 or 211**	**155 or 239**	**183 or 267**	**Last treatment + 30 days**
Time (post-dose)	**-**		**-**	**-**		**-**	**-**	**-**	**-**

Table 8-4 Details for highly repetitive assessments, Cohort B

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8.1 Screening

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

In the case where a safety laboratory assessment at screening and/or initial baseline is more than 10% outside of the range specified in the exclusion criteria, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the subject must be excluded from the study.

Information on what data must be collected for screening failures and further information on re-screening is outlined in the Site Operations Manual.

8.1.1 Information to be collected on screening failures

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

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. 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.

8.2.1 Hepatitis screen, HIV screen

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

8.2.2 Tuberculosis status

Determination of tuberculosis status will be required before administration of study treatment. Any significant findings will be recorded in the “Relevant medical history/Current medical conditions” section of the eCRF.

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

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8.2.4 Renal Biopsies for screening evaluation

For kidney native patients in Cohort A of the study, the diagnosis of C3G must be based on a renal biopsy not older than 12 months. In case of an older biopsy patients will be asked to perform a new renal biopsy during the run-in period to confirm eligilibity. More details are outlined in the Site Operations Manual.

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For patients transplanted, C3G diagnosis should be supported by specific documentation. More details on biopsies collection for Cohort B patients are reported in Section 8.3.3 under Efficacy section.

8.3 Efficacy/Pharmacodynamics

Efficacy / Pharmacodynamic samples will be collected at the time points defined in the Assessment schedule (refer to Table 8-1 and Table 8-3). Follow instructions outlined in the Site Operations Manual regarding sample collection, numbering, processing and shipment.

Pharmacodynamic (PD) samples will be obtained and evaluated in all subjects at all dose levels.

8.3.1 Appropriateness of efficacy assessments

- Primary endpoint Cohort A: Reduction in proteinuria from baseline at Week 12. 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 is considered sufficient to see relevant treatment effect on the selected primary endpoint based on literature (Fellström et al 2017) and guidelines (KDIGO 2012).
- Primary endpoint Cohort B: Change from baseline in C3 Deposit Score (based on immunofluorescence microscopy). This endpoint will be assessed by a score comprising reduction in C3 deposition assessed by immune fluorescence staining. This endpoint was chosen since renal C3 deposition is required to establish C3G diagnosis. Further C3 deposition is directly linked to C3G pathophysiology and considered causal to renal impairment.
- Secondary endpoints for Cohort A and B: Complement biomarkers (e.g. Bb, C3 in serum) to assess the pharmacodynamic effect at different doses of LNP023. For C3G, the underlying mechanism causing renal disease is dysregulation of complement AP C3- and C5- convertase. LNP023 is expected to block the dysregulation and thereby should normalize complement biomarker levels in serum. Therefore, assessment of the effect of LNP023 on complement biomarkers should identify doses that would be expected to be efficacious for treatment of this disease. Bb and C3 are biomarkers that accurately reflect the level of complement AP activation. Complement biomarkers are therefore considered to be sensitive and accurate estimates of target engagement

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8.3.2 24-hours urine collection

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Measurement includes UPCR and UACR, 24-h UP and 24-h UA, creatinine clearance, hematuria and PK (only during treatment period visits). Samples may also be used to assess urine protein size profiles to explore kidney damage.

Refer to SOM for more details.

8.3.3 Renal Biopsies for efficacy evaluation

To assess histopathological changes in kidney biopsies of patients transplanted in Cohort B of the study, a renal biopsy will be collected any time during run-in period as baseline, if the most recent biopsy is older than 3 months. A renal biopsy has to be collected at Week 12.

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8.3.4 Glomerular filtration rate

Estimated glomerular filtration rate (eGFR) is calculated applying the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation) (Levey et al 2009).

$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018\ [\text{if female}] \times 1.159\ [\text{if black}]$

where: S_{cr} is serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of S_{cr}/κ or 1, and max indicates the maximum of S_{cr}/κ or 1.

The equation does not require weight because the results are reported normalized to 1.73 m^2 body surface area, which is an accepted average adult surface area.

8.3.5 Pharmacodynamic Assessments

Pharmacodynamic assessments are specified below, with the methods for assessment and recording specified in the SOM. Assessments will be performed/samples collected at the timepoints defined in the Assessment Schedule (refer to Table 8-1 and Table 8-3).

8.3.5.1 Renal Parameters

The pharmacodynamic effect of LNP023 is assessed analysing the following renal parameters:

- UA, UACR, UP, UPCR, serum creatinine, creatinine clearance, eGFR, hematuria
- Ratio to baseline of UPCR and UACR derived from 24-h urine collection

8.3.5.2 Complement pathway biomarkers

Soluble complement biomarkers in circulation and urine 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)
- C3
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8.3.6 First morning void urine collection

First morning void urine will be collected Commercially Confidential Information (refer to Table 8-1 and Table 8-3).

Measurement includes UPCR and UACR, UP and UA, hematuria.

Refer to SOM for more details.

8.4 Safety

Safety assessments are specified below with the Assessment schedule (refer to Section 8) detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to Section 10.1.

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

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to Investigators in the Laboratory Manual.

Clinically significant abnormalities must be recorded on the relevant section of the medical history/Current medical conditions/AE CRF / e(CRF) page as appropriate.

8.4.1.1 Blood Chemistry

Albumin, Alkaline phosphatase, ALT , AST , Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Cystatin C (Cys C), Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL-C, HDL-C, Triglycerides, Total Protein, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose, CK-MB, VLDL-C and non HDL-C, (hs)CRP.

8.4.1.2 Hematology

Hemoglobin, hematocrit, red blood cell (RBC) count, CCI white blood cell (WBC) count with differentials and platelet count will be measured. Coagulation testing including prothrombin time (PT) also reported as INR and activated partial thromboplastin time (aPTT) will be measured.

8.4.1.3 Urinalysis and Urine Microscopy

Dipstick measurements for leucocytes, protein, blood will be performed. Any positive result, atypical for a C3G patient, will require a sample to be sent for further microscopy assessment of WBC, RBC and sediments. Results for both the positive dipstick parameters and the microscopy will be recorded in the appropriate eCRFs.

8.4.2 Electrocardiogram (ECG)

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

All ECGs are done as 12-lead triplicate ECGs. All ECG 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).

Clinically significant abnormalities must be reported in the AE CRF.

8.4.3 Pregnancy and assessments of fertility

Pregnancy Testing

All pre-menopausal women who are not surgically sterile will have pregnancy testing. See the Assessment schedule (Section 8), for timing of the protocol required pregnancy testing in serum or urine; additional pregnancy testing may be performed to meet local requirements*. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative.

*Additional pregnancy testing might be performed if requested per local requirements.

Refer to Section 10.1.4 for details on Reporting Pregnancy.

Assessments of Fertility

Refer to Section 5.2 for criteria to determine women that are not of child bearing potential.

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documentation. 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:

- surgical bilateral oophorectomy without a hysterectomy
- reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

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8.4.4 Vital Signs

8.4.4.1 Pulse Rate

Pulse rate will be measured as per Assessment Schedule, refer to SOM for more details.

8.4.4.2 Blood Pressure

Systolic and diastolic blood pressure will be measured using an automated validated device with an appropriately sized cuff. 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.

The repeat sitting measurements will be made at up to 5 minute intervals and measurements will be recorded on the Vital Signs eCRF.

Refer to SOM for more details.

8.4.4.3 Body Temperature

Body temperature should be measured as per local practice – the same method to be used consistently for all patients at each site.

Refer to SOM for more details.

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8.4.7 Physical Examination

A complete physical examination should include the examination of general appearance, skin, neck CCI , eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological systems. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed. Information for all physical examinations must be included in the source documentation at the study site and will not be recorded on the eCRF. Significant findings that are present prior to informed consent are included in the CRF capturing Medical History. Significant findings observed after informed consent signature which meet the definition of an AE must be appropriately recorded on the appropriate CRF capturing AEs.

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8.4.9 Vaccination

If prior vaccination cannot be confirmed e.g. documented in subject's medical notes, subjects enrolling must be vaccinated against *N. meningitidis*, *S. pneumoniae* and *H. influenza*. To ensure full protection, the vaccines against *N. meningitidis* should cover the most common serotypes.

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Continuous close monitoring of subjects for early symptoms and signs of meningococcal infection is required in order to evaluate subjects immediately if an infection is suspected.

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8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

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8.5.2 Pharmacokinetics

PK samples will be collected at the time points defined in the Assessment schedule. The exact time point need to be recorded as well as missing samples.

Pharmacokinetic (PK) samples will be obtained and evaluated in all subjects at all dose levels.

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For standard pharmacokinetic abbreviations and definitions see the list provided at the beginning of this protocol.

The following pharmacokinetic parameters of LNP023 will be determined using the actual recorded sampling times and non-compartmental analysis method(s) with Phoenix WinNonlin (Version 6.4 or higher):

Plasma: Cmax, Tmax,, AUClast, AUCtau and Ctrough (Cmin) after the first dose on Day 7, Day 14, Day 21 and Day 28 as well as Cmin on Days 92 and 99 (Week 13 and 14)

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Urine: Non-compartmental parameters, including but not limited to total cumulative urinary excretion (Ue) and renal plasma clearance (CLr) of LNP023.

Other pharmacokinetic parameters may be calculated as appropriate. All parameters determined are considered at steady state.

The linear trapezoidal rule will be used for AUC calculation. AUCtau will be calculated instead of AUCinf. Values below the lower limit of quantification will be treated as zero for calculation of PK parameters as well as for summary statistics.

Further details on sample collection, numbering, processing and shipment will be provided in the lab manual and/or SOM.

8.5.3 Biomarkers

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9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment 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 return for the assessments indicated by an asterisk (*) in the assessment table (safety follow up and end of study visits). 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.

Cohort A

Study treatment 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 efficiently manageable while being on LNP023
- Worsening of C3G disease
- Use of prohibited treatment as outlined in Table 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

Cohort B

Study treatment must be discontinued under the same circumstances as Cohort A plus the below:

- Histologic signs of graft rejection ≥ 2A BANFF and other signs of graft rejection that require increased doses of concomitant immunosuppressive therapies.

9.1.1.1 Replacement policy

Not applicable.

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

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.

9.1.3 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.

9.1.4 Study stopping rules

Novartis 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 LNP023 (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 patient(s) with LNP023 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 LNP023
- OR two or more SAEs that are considered by the Investigator as potentially related to LNP023.

The study may resume following the safety review, if the Investigator and Sponsor agree it is safe to proceed. Restart of this clinical trial in such case will be documented by a substantial amendment and following approval by relevant health authorities.

The Sponsor could decide to stop the enrollment for early success in Cohort A in case 50% will have normal C3 blood levels (≥ 900 mg/L) at Week 12.

9.1.5 Early study termination by the sponsor

The study can be terminated by the Sponsor 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, Sponsor will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible (provide instruction for contacting the subject, when the subject should stop taking drug, when the subject should come for a final visit) 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 his/her 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.

In case patients will roll-over in the extension study, study completion will occur at Visit 190

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All treated patients should have a safety follow-up call conducted 30 days after last administration of study treatment. The information collected is 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 based on subject availability for follow-up. This care may include enrollment in an extension study, once available.

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 subjects and identifying adverse events.

Sponsor 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 in the Adverse Events CRF 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 (refer to Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding 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
- its outcome
  a) not recovered/not resolved;
  b) recovered/resolved;
  c) recovering/resolving;
  d) recovered/resolved with sequelae;
  e) 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 SOM 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.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

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.

Consider the following 3 categories (as applicable) to determine SAE reporting timeframes:

1. 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.
2. Run-in Failures: SAEs collected between time subject signs ICF until time that subject is determined to be a run-in failure.
3. Treated Subjects: SAEs collected between time subject signs ICF until 30 days after the subject has discontinued or stopped study treatment (or longer, depending on the elimination half-life of LNP023).

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. The Sponsor 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 intervention or-treatment follow-up visits with no required procedures should only be reported to Sponsor Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Sponsor 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 Sponsor 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 collected in the DAR (dose administration record) eCRF 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 Dose Administration (DAR) eCRF (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 completion of the standard base liver CRF pages

Please refer to Table 16-1 in Appendix 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 (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 reported on the unplanned local laboratory CRF (or liver CRF page)
- 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 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 the procedures performed must be recorded as appropriate in the CRF.

Refer to the Site Operations Manual for additional details.

10.2.2 Renal safety monitoring

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

10.2.3 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.

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Other additional evaluations will be performed at the discretion of the Investigator.

11 Data Collection and Database management

11.1 Data collection

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

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, imaging) 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 the vendor working on behalf of Novartis.

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.

11.2 Database management and quality control

Sponsor 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 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.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Sponsor development management.

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11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Sponsor or delegated CRO representative will review the protocol and data capture requirements (i.e., eSource DDE or eCRFs) with the investigators and their staff. During the study, Sponsor 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 Sponsor or delegated CRO or CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Sponsor 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. Sponsor 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

Any data analysis carried out independently by the investigator should be submitted to Sponsor before publication or presentation. The data analysis includes data generated from Screening, Treatment period CCI and safety Follow-up periods

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12.1 Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received for Cohort A and B.

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

The PK analysis set will include all subjects with available PK data and no protocol deviations with relevant impact on PK data.

The PD analysis set will include all subjects with available PD data and no protocol deviations with relevant impact on PD data.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed by subject and summarized descriptively for all subjects for the safety set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized (separately) by system organ class and preferred term, for all subjects.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by subject.

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, 25th and 75th percentiles, minimum, and maximum will be presented.

Data for study drug administration will be listed by subject and summarized by treatment group.

Summary includes:

- Number of subjects who took all the planned doses of LNP023

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, for all subjects.

12.4 Analysis of the primary endpoint(s)

The primary objectives of this study are:

Cohort A: To evaluate the efficacy of LNP023 in reducing proteinuria at week 12, as assessed by Ratio to baseline of Urine Protein to Creatinine concentration Ratio derived from 24-h urine collection in C3G patients who have not received a kidney transplantation and have reduced C3 blood levels.

Cohort B: To assess histopathological changes in kidney biopsies at Week 12, as assessed by change from baseline in C3 Deposit Score (based on immunofluorescence microscopy) in C3G patients who have received a kidney transplantation.

12.4.1 Definition of primary endpoint(s)

The primary endpoints of this study are

Cohort A: Reduction from baseline in UPCR at Week 12

Cohort B: Change from baseline in C3 Deposit Score (based on immunofluorescence microscopy) at Week 12

12.4.2 Statistical model, hypothesis, and method of analysis

12.4.2.1 Statistical Analysis:

Cohort A

The primary variable for assessing the effect of LNP023 is the log ratio to baseline UPCR derived from the 24h urine collections at Week 12.

A mixed model repeated measures (MMRM) will be fitted to the log ratio to baseline UPCR values over time. The model will include the log ratio to baseline UPCR as the dependent variable, time point (as study day relative to the start of study treatment) as a fixed effect, and baseline log transformed UPCR as a fixed covariate.

Baseline is defined to be the 24h urine collection on Day -1 to Day 1. An unstructured covariance matrix will be used.

Results from this modelling will be presented as the estimated mean value of log UPCR at week 12 together with the 80% confidence interval. The results will be back transformed to provide the geometric mean and their 80% CIs on the original scale.

Cohort B

The primary variable for assessing the histopathological changes in kidney biopsies is week 12 change from baseline C3 Deposit Score.

The Wilcoxon signed rank test will be used for C3 Deposit Score data at Week12 time point to compare the median difference of change from baseline. The Hodges-Lehmann estimate and 80% confidence interval for the median difference will be provided.

12.4.3 Handling of missing values/censoring/discontinuations

The primary analysis will include all available data up to the point of treatment discontinuation for patients who discontinue.

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Subjects with missing UPRC or C3 Deposit Score values will still be included in the mixed model analysis with such data assumed missing at random (MAR).

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Given the severe nature of the indication and the need for close monitoring it is expected that there will be very little truly missing data.

12.4.4 Sensitivity analyses

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12.5 Analysis of secondary endpoints

The secondary variables supporting the secondary objective are provided below:

Biomarkers:

Including blood levels of C3, Bb.

PD variables:

- urine UPCR.
- Renal parameters UA, UACR, UP, UPCR, serum creatinine, eGFR (using the CKD-EPI formula), creatinine clearance, hematuria.
- Ratio to baseline of UPCR and UACR derived from 24-h urine collection

Safety variables:

- ECG, vital signs, safety laboratory assessments CCI , AEs and SAEs.

PK variables:

Total drug PK parameters, including Tmax, Cmax, AUClast and AUCtau, as well as Ctrough (pre-dose) after multiple doses and total cumulative urinary excretion (Ue) and renal plasma clearance (CLr).

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

The secondary variables supporting the secondary objective to assess the effect of LNP023 on renal function are 24-h UA, UACR, 24-h UP, UPCR, serum creatinine, eGFR, creatinine clearance, hematuria.

These variables will each be analyzed with the same MMRM as used for the primary variable.

Additionally the ratio to baseline of UPCR and UACR derived from 24-h urine collection will also be analyzed with the same MMRM (only Cohort B).

Appropriate transformations will be detailed in the SAP.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by subject.

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 addition, a separate summary for death including on-treatment and post-treatment deaths will be provided. 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 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.

Adverse events

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

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 and adverse events leading to dose adjustment.

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.

Vital signs

All vital signs data will be listed by treatment group, patient, and visit/time and if ranges are available, abnormalities will be flagged.

Summary statistics will be provided by treatment and visit/time.

12-lead ECG

All ECG data will be listed by treatment group, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time and the number of patients with values above key threshold values will be displayed.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, subject, and visit/time and if normal ranges are available abnormalities will be flagged.

Summary statistics will be provided 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.

Other safety evaluations

Include or omit as relevant for any additional safety parameters – describe the listings, summaries and/or graphical output.

12.5.3 Pharmacokinetics

Individual LNP023 plasma/urine concentration data will be listed by treatment, subject, and visit/sampling time point, and plotted over time by subject.

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Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum.

Commercially Confidential Information A geometric mean will not be reported if the dataset includes zero values.

All individual plasma concentration-time profiles for LNP023 concentration with median will be displayed graphically by treatment on semi-log view. In addition, the mean (+/- SD) and

geometric mean plasma concentration-time profiles for LNP023 by treatment over time will be displayed graphically on the linear and semi-log view.

Pharmacokinetic parameters will be calculated as described in Section 8.5.2 and will be listed by treatment and subject.

Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented.

12.5.4 Biomarkers

All biomarker data (except for hypothesis-free platforms) will be listed by treatment, subject, and time. Summary statistics will be provided by treatment and time.

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Graphical measures will be used to explore relationships between LNP023 treatment and biomarkers.

Additionally graphical measures will be used to assess the relationships between changes in proteinuria and biomarker over time.

12.5.5 PK/PD relationships

Efficacy biomarkers analysed during this study will be plotted against individual PK parameters such as Cmax or AUC as well as against administered dose to establish the exposure/ response relationship and to determine the (lowest) efficacious dose or exposure.

12.6 Analysis of exploratory endpoints

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12.7 Interim analyses

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12.8 Sample size calculation

12.8.1 Primary endpoint(s)

Cohort A - Primary Endpoint: Reduction from baseline in log transformed UPCR.

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a sample size of 15 subjects provides 93% power that the primary analysis will be statistically significant at the one-sided 10% significance level assuming 20% of losses to follow-up.

Cohort B - Primary Endpoint: Change from baseline in C3 Deposit Score (based on immunofluorescence microscopy).

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a sample size of 12 subjects provides 94% power that the primary analysis will be statistically significant at the one-sided 10% significance level assuming 17% of losses to follow-up.

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 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 Sponsor 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, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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16 Appendices

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