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LNP023

Clinical Trial Protocol CLNP023X2201 / NCT03439839

An open label, single arm, multiple dose study to assess efficacy, safety, pharmacokinetics and pharmacodynamics of LNP023 when administered in addition to Standard of Care (SoC) in patients with paroxysmal nocturnal hemoglobinuria (PNH) with signs of active hemolysis

Document type:	Amended Protocol Version
EUDRACT number:	2017-000888-33
Version number:	v05 (Clean)
Clinical Trial Phase:	II
Release date:	26-Jul-2021

Site Operations Manual (SOM)

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

Notification of serious adverse events

Dear Investigator,

You must report a serious adverse event (SAE) (initial or follow-up) to Novartis as summarized below. Refer to Section 9.2 of the protocol for SAE criteria and additional requirements. See also page 2 of the Site Operations Manual for further details on the method of reporting a SAE.

- Complete SAE report
- Submit SAE report to Chief Medical Office and Patient Safety (CMO & PS) **within 24 hours after awareness of the SAE**
- Notify the Novartis Medical Lead
- The fax number(s) and email address(es) are located in the Site Operations Manual.

Table of contents

Site Operations Manual (SOM) 2
Notification of serious adverse events 2
Table of contents 3
List of tables 8
List of figures 8
List of abbreviations 9
Pharmacokinetic definitions and symbols 13
Glossary of terms 14

Commercially Confidential Information (CCI)

Protocol summary 23
1 Introduction 28
1.1 Background 28
1.2 Nonclinical data 29

Commercially Confidential Information

1.3 Clinical data 31

Commercially Confidential Information

1.4 Study purpose 33
2 Objectives and endpoints 33
2.1 Primary objective(s) 33
2.2 Secondary objective(s) 33
2.3 Exploratory objective(s) 34
3 Investigational plan 34
3.1 Study design 34
3.2 Rationale of study design 36
3.3 Rationale for dose/regimen, route of administration and duration of treatment 37
3.4 Rationale for choice of comparator 38
3.5 Rationale for choice of background therapy 38
3.6 Purpose and timing of interim analyses/design adaptations 38

3.7 Risks and benefits 39
3.7.1 General 39
3.7.2 Potential risks 39
3.7.3 Blood sample volumes 42
3.7.4 Risk mitigation strategy 43
3.7.5 Rationale for Public Health Emergency mitigation procedures 43
4 Population 44
4.1 Inclusion criteria 44
4.2 Exclusion criteria 45
5 Restrictions for Study Subjects 47
5.1 Contraception requirements 47
5.2 Prohibited treatment 47
5.3 Dietary restrictions and smoking 48
5.4 Other restrictions 48
6 Treatment 49
6.1 Study treatment 49
6.1.1 Investigational treatment and control drug(s) 49
6.1.2 Bio-batch retention samples 49
6.1.3 Additional study treatment 49
6.2 Treatment arms 50
6.3 Treatment assignment and randomization 50
6.4 Treatment blinding 50
6.5 Treating the subject 50
6.6 Permitted dose adjustments and interruptions of study treatment 51
6.7 Emergency breaking of assigned treatment code 51
6.8 Treatment exposure and compliance 51
6.9 Recommended treatment of adverse events 51
6.10 Rescue medication 51
6.11 Concomitant treatment 52
7 Study completion and discontinuation 53
7.1 Study completion and post-study treatment 53
7.2 Discontinuation of study treatment 53
7.3 Withdrawal of informed consent 54
7.4 Lost to follow-up 55
7.5 Study stopping rules 55
7.6 Early study termination by the sponsor 55
8 Procedures and assessments 56

8.1 Assessment schedule 56
8.2 Informed consent procedures 61
8.3 Subject screening 62
8.4 Subject demographics/other baseline characteristics 62
8.4.1 PNH clone size 62
8.4.2 Demography 62
8.4.3 Medical history/current medical conditions 62
8.4.4 Pregnancy and assessments of fertility 62
8.5 Efficacy / Pharmacodynamics 63
8.5.1 LDH 63
8.5.2 C3 fragment deposition and PNH-type red blood cells 63
8.6 Safety 64
8.6.1 Electrocardiogram (ECG) 64
8.6.2 Clinical Chemistry 64
8.6.3 Hematology 65
8.6.4 Markers of thrombosis 65
8.6.5 Urinalysis 65
8.6.6 Patient diary 65
8.6.7 Vital signs and body measurements 65
8.6.8 Physical Examination 66
8.6.9 Vaccinations 66
8.6.10 Incidence of transfusion 66
8.6.11 Patient reported outcomes 66
8.7 Pharmacokinetics 66
8.8 Other assessments 67
8.8.1 Exploratory biomarkers in serum 67
8.8.2 Exploratory biomarkers in plasma 68
Commercially Confidential Information
8.9 Use of residual biological samples 68
9 Safety monitoring 69
9.1 Adverse events 69
9.2 Serious adverse event reporting 70
9.2.1 Definition of SAE 70
9.2.2 SAE reporting 71
9.3 Liver safety monitoring 73
9.4 Reporting of study treatment errors including misuse/abuse 73
9.5 Pregnancy reporting 74

9.6 Early phase safety monitoring 74
10 Data review and database management 75
10.1 Site monitoring 75
10.2 Data collection 75
10.3 Database management and quality control 76
10.4 Data Monitoring Committee 76
10.5 Adjudication Committee 77
11 Data analysis 77
11.1 Analysis sets 77
11.2 Subject demographics and other baseline characteristics 77
11.3 Treatments 77
11.4 Analysis of the primary variable(s) 77
11.4.1 Primary Variable(s) 77
11.4.2 Statistical model, hypothesis, and method of analysis 78
11.4.3 Handling of missing values/censoring/discontinuations 78
11.4.4 Sensitivity analyses 79
11.5 Analysis of secondary variable(s) 79
11.5.1 Efficacy / Pharmacodynamics 79
11.5.2 Safety 79
11.5.3 Pharmacokinetics 80
11.5.4 Pharmacokinetic / pharmacodynamic interactions 80
11.5.5 Other assessments 80
11.6 Analysis of exploratory variables 80
11.6.1 Exploratory biomarkers 80
Commercially Confidential Information
11.6.3 Other Exploratory biomarkers 81
11.7 Sample size calculation 81
11.8 Power for analysis of key secondary variables 81
11.9 Interim analyses 81
12 Ethical considerations 82
12.1 Regulatory and ethical compliance 82
12.2 Responsibilities of the investigator and IRB/IEC 82
12.3 Publication of study protocol and results 82
12.4 Quality Control and Quality Assurance 82
13 Protocol adherence 83
13.1 Protocol Amendments 83
14 References 84

15 Appendix 1: Liver Event Definitions and Follow-up Requirements.....86
16 Appendix 2: Specific Renal Alert Criteria and Actions.....88

List of tables

Table 5-1 Prohibited medication 48
Commercially Confidential Information
Table 8-1 Assessment Schedule 57
Table 9-1 Guidance for capturing study treatment errors 74
Table 15-1 Liver Event Definitions 86
Table 15-2 Actions required for Liver Events 86
Table 15-3 Exclusion of underlying liver disease 87
Table 16-1 Specific Renal Alert Criteria and Actions 88
Table 16-2 Follow-up of renal events 89

List of figures

Figure 3-1 Study design 36
Figure 11-1 Forest plot of LDH final mean estimates at from 6 studies of various lengths 78

List of abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibodies
AP	Alternative Pathway
aPTT	Activated Partial Thromboplastin Time
AhR	Aryl Hydrocarbon Receptors
ASMA	Anti-Smooth Muscle Antibodies
AST	Aspartate Aminotransferase
b.i.d.	bis in die (twice a day)
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CFR	U.S. Code of Federal Regulations
CK	Creatinine Kinase
CMO	Chief Medical Office
CMO&PS	Chief Medical Office & Patient Safety
CO_2	Carbon Dioxide
CRF	Case Report/Record Form (Paper or Electronic)
CRO	Contract Research Organization
CT	Computerized Tomography
CTC	Common Toxicity Criteria
CV	Coefficient of Variation
CYP2C8	Cytochrome P4502C8
CYP450	Cytochrome P450
DDI	Drug-Drug Interactions
DHT	Dihydrotestosterone
DRF	Dose Range Finding
ECG	Electrocardiogram
eCRF	Electronic Case Report Form (s)
EDC	Electronic Data Capture
EOS	End of Study

EoT	End of Treatment
eSource	Electronic Source
FACIT	Functional Assessment of Chronic Illness Therapy
FB	Factor B
FDA	Food and Drug Administration
FE	Food Effect
FIH	First In Human
FIR	First Interpretable Results
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GLP	Good Laboratory Practice
GPI	Glycosylphosphotatidylinositol
h	Hour
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HV	Healthy Volunteers
i.v.	intravenous
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine System
LDH	Lactate Dehydrogenase

LFT	Liver Function Test
LH	Luteinizing Hormone
LLN	Lower Limit of Normal

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LOAEL	Lowest Observed Adverse Effect Level
MABEL	Minimum Anticipated Biological Effect Level
MAC	Membrane Attack Complex
MAD	Multiple Ascending Dose
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
mL	Milliliter(s)
MMF	Mycophenolate Mofetil
MMRM	Mixed Model Repeated Measures
MRI	Magnetic Resonance Imaging
NOAEL	No Observed Adverse Effect Level
NYHA	New-York Heart Association
OATP	Organic Anion-Transporting Polypeptide
OC	Oral Contraceptives
P-gp	Permeability Glycoprotein
p.o.	Oral
PA	Posteroanterior
PC	Personal Computer
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PNH	Paroxysmal Nocturnal Hemoglobinuria
PRO	Patient Reported Outcome(s)
PS	Patient Safety
PXR	Pregnane X Receptor
PSD	Premature Subject Discontinuation
PT	Prothrombin Time
q.d.	Once daily

RAP	Reporting and Analysis Process
RBC	Red Blood Cell(s)
REP	Roll-over Extension Program
s.c.	Subcutaneous
SAD	Single Ascending Dose
SAE	Serious Adverse Event
sCR	Serum Creatinine
SD	Standard Deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SoC	Standard of Care
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
T3	Triiodothyronine
T4	Thyroxine
TBL	Total Bilirubin
TD	Study Treatment Discontinuation
TDI	Time Dependent Inhibition
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
ULQ	Upper Limit of Quantification
US	Ultrasound
WBC	White Blood Cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent
WOCBP	Women of Child Bearing Potential
β-hCG	Beta-Human Chorionic Gonadotropin

Pharmacokinetic definitions and symbols

Ae0-t	Amount of drug (or defined metabolite) excreted into the urine from time zero to time 't' where t is a defined time point after administration [mass units or % of dose]
AUC0-t	The area under the plasma (or serum or blood) concentration-time curve from time zero to time 't' where t is a defined time point after administration [mass x time / volume]
AUCinf	The area under the plasma (or serum or blood) concentration-time curve from time zero to infinity [mass x time / volume]
AUClast	The area under the plasma (or serum or blood) concentration-time curve from time zero to the time of the last quantifiable concentration [mass x time / volume]
AUCtau	The area under the plasma (or serum or blood) concentration-time curve from time zero to the end of the dosing interval tau [mass x time / volume]
AUCtau,ss	The area under the plasma (or serum or blood) concentration-time curve from time zero to the end of the dosing interval tau at steady state [mass x time / volume]
Cav,ss	The average steady state plasma (or serum or blood) concentration during multiple dosing
CL/F	The apparent systemic (or total body) clearance from plasma (or serum or blood) following extravascular administration [volume / time]
CLr	The renal clearance from plasma (or serum or blood) [volume / time]
Cmax	The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume]
Cmax,ss	The observed maximum plasma (or serum or blood) concentration following drug administration at steady state [mass / volume]
Cmin,ss	The lowest plasma (or serum or blood) concentration observed during a dosing interval at steady state [mass / volume]
Racc	The accumulation ratio
T1/2	The terminal elimination half-life [time]
T1/2,acc	The effective half-life based on drug accumulation at steady state [time]
Tmax	The time to reach the maximum concentration after drug administration [time]
Vss/F	The apparent volume of distribution at steady state following extravascular administration [time]
Vz/F	The apparent volume of distribution during the terminal elimination phase following extravascular administration [volume]

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.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Hemolysis	The rupturing or lysis of red blood cells leading to the release of the cells contents into the surrounding fluid.
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”
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.

Patient	An individual with the condition of interest
Personal Data	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
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent	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	CLNP023X2201
Full Title	An open label, single arm, multiple dose study to assess efficacy, safety, pharmacokinetics and pharmacodynamics of LNP023 when administered in addition to Standard of Care (SoC) in patients with paroxysmal nocturnal hemoglobinuria (PNH) with signs of active hemolysis
Brief title	Efficacy, safety, pharmacokinetics and pharmacodynamics study of LNP023 in patients with paroxysmal nocturnal hemoglobinuria
Sponsor and **Clinical Trial Phase**	Novartis Phase II
Intervention type	Drug
Study type	Interventional
Purpose and rationale	LNP023 is a novel oral small molecular weight compound, with first-in-class potential, that inhibits factor B (FB) of the alternative pathway (AP). Blockade of the AP with oral LNP023 has the potential to prevent both intra - and extravascular hemolysis and may, therefore, offer therapeutic superiority to the existing eculizumab Standard of Care (SoC) therapy that currently require intravenous (i.v.) infusions every second week. The main purpose of this study is to evaluate the efficacy of LNP023 in patients with PNH, showing signs of active hemolysis despite treatment with SoC (defined as an antibody with anti C5 activity).
Primary Objective(s)	To assess the effect of LNP023 on the reduction of chronic hemolysis in PNH patients when administered in addition to SoC (monoclonal antibody with anti C5 activity).
Secondary Objectives	To assess the safety and tolerability of LNP023 in patients with PNH when administered in addition to SoC (monoclonal antibody with anti C5 activity). To assess the effect of LNP023 on markers of intra and extravascular hemolysis when administered in addition to SoC (monoclonal antibody with anti C5 activity) To assess the plasma PK of LNP023 in PNH patients

Study design	This is a non-confirmatory, open label, multiple dose study in patients with PNH. Two cohorts will be included into the study. Assessment schedule will be identical for both cohorts. For Cohort 1 (approximately 10 patients) this study includes: • a screening period of up to 68 days, • a baseline visit, • Treatment Part 1: 13 weeks of treatment with 200 mg LNP023 b.i.d. administered orally in addition to SoC, • Treatment Part 2: Treatment extension for approximately 2 to 3 years with the same treatment regimen as used in Part 1 in patients who benefit from LNP023 treatment in Part 1 (see Section 4.1). Note that patients can complete Part 2 any time after a minimal total duration of LNP023 treatment of 2 years (i.e., after V130) without being considered early discontinuations, for example, to transition to the roll-over extension program (REP), • Commercially Confidential Information • an End of Study (EoS) visit 2 weeks after last LNP023 administration for patients not joining the REP; for patients joining the REP, the last treatment visit will become the EoS visit. • a safety follow-up call conducted 30 days after last administration of study treatment (applicable only for patients not joining the REP). For Cohort 2 (approximately 5 patients) this study includes: • a screening period of up to 68 days, • a baseline visit, • Treatment Part 1: Minimum of 2 weeks of treatment with CCI LNP023 b.i.d. administered orally in addition to SoC. CCI Commercially Confidential Information • Treatment Part 2: Treatment extension for approximately 2 to 3 years with the same treatment regimen as used in Part 1 in patients who benefit from LNP023 treatment in Part 1 (see Section 4.1). For patients receiving CCI the dose may be escalated as described for Part 1. Note that patients can complete Part 2 any time after a minimal total duration of LNP023 treatment of 2 years (i.e., after V130) without being considered early discontinuations, for example, to transition to the roll-over extension program (REP), • Commercially Confidential Information • an End of Study (EoS) visit 2 weeks after last LNP023 administration for patients not joining the REP; for patients joining the REP, the last treatment visit will become the EoS visit. • a safety follow-up call conducted 30 days after last administration of study treatment (applicable only for patients not joining the REP). For all patients:

	• The baseline visit can be skipped if Screening and Day 1 visit are not more than 7 days apart (Figure 3-1). If possible, study visits should be aligned with SoC administration. On Day 1 and any other visits when both SoC and LNP023 are administered, LNP023 is administered prior to SoC. • The expected study duration is between approximately 2.5 and 3.5 years.
Population	Up to 15 PNH patients with signs of active hemolysis will be included in the study.
Key Inclusion criteria	• Written informed consent must be obtained before any assessment is performed. • Male and female patients between the age of 18-80 (inclusive) at baseline with a diagnosis of PNH based on documented clone size of ≥10% by RBCs and/or granulocytes, measured by GPI-deficiency on flow cytometry (screening or medical history data acceptable). • For Cohort 1 only: LDH values ≥ 1.5x upper limit of the normal range for at least 3 pre-SoC dosing measurements taken in relation to 3 different SoC dosing dates over a maximum of 10 weeks prior to Day 1 (screening, baseline or medical history data acceptable). All other screening pre-SoC LDH values have to be >1x upper limit of normal range (for pre-SoC samples collected at the same day as SoC administration). • For Cohort 2 only: LDH values ≥ 1.25x upper limit of the normal range for at least 3 pre-SoC dosing measurements taken in relation to 3 different SoC dosing dates over a maximum of 10 weeks prior to Day 1 (screening, baseline or medical history data acceptable). All other screening pre-SoC LDH values have to be >1x upper limit of normal range (for pre-SoC samples collected at the same day as SoC administration). • For Cohort 2 only: Hemoglobin level <10.5 g/dL at baseline. • PNH patients on stable regimen of standard of care complement blockade (monoclonal antibody with anti C5 activity) for at least 3 months prior to first treatment with LNP023. • Previous vaccination against Neisseria meningitidis types A, C, Y and W-135 is required at least 4 weeks prior to first dosing with LNP023. Vaccination against N. meningitidis type B should be conducted if available and acceptable by local regulations, at least 4 weeks prior to first dosing with LNP023. If LNP023 treatment has to start earlier than 4 weeks post vaccination, prophylactic antibiotic treatment must be initiated. • Previous vaccination for the prevention of S. pneumoniae and H. influenzae at least 4 weeks prior to first dosing with LNP023. If LNP023 treatment has to start earlier than 4 weeks post vaccination, prophylactic antibiotic treatment must be initiated. • Able to communicate well with the investigator, to understand and comply with the requirements of the study. • For Part 2 of the study, patients who as per judgment of Investigator benefit from LNP023 treatment based on reduced hemolytic parameters as compared to Screening and Baseline.

Key Exclusion criteria	• Participation in any other investigational drug trial or use of other investigational drugs at the time of enrollment, or within 5 elimination half-lives of enrollment, or within 30 days, whichever is longer; or longer if required by local regulations • Known or suspected hereditary complement deficiency at screening • History of hematopoietic stem cell transplantation as verified both at screening and at baseline (unless baseline was skipped) • Patients with laboratory evidence of bone marrow failure (reticulocytes <60x10E9/l, platelets <30x10E9/l neutrophils <1x10E9/l) as verified both at screening and at baseline (unless baseline was skipped) • A positive HIV, Hepatitis B (HBV) or Hepatitis C (HCV) test result at screening • Presence or suspicion (based on judgment of the investigator) of active infection within 2 weeks prior to first dose of LNP023, or history of severe recurrent bacterial infections • History of recurrent meningitis, history of meningococcal infections despite vaccination as verified both at screening and at baseline (unless baseline was skipped) • Patients on the immunosuppressive agents such as but not limited to cyclosporine, MMF, tacrolimus, cyclophosphamide, methotrexate less than 8 weeks prior to first treatment with LNP023 unless on a stable regimen for at least 3 months prior to first LNP023 dose. • Systemic corticosteroids administered at the dose of ≥ 10 mg per day prednisone equivalent within less than 4 weeks prior to first treatment with LNP023 • Severe concurrent co-morbidities, e.g. patients with severe kidney disease (dialysis), advanced cardiac disease (NYHA class IV), severe pulmonary arterial hypertension (WHO class IV), unstable thrombotic event not amenable to active treatment as judged by the investigator both at screening and at baseline (unless baseline was skipped) • Any medical condition deemed likely to interfere with the patient's participation in the study, or likely to cause serious adverse events during the study • Female patients who are pregnant or breastfeeding, or intending to conceive during the course of the study • Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception from first dosing with LNP023 until EOS.
Study treatment	• LNP023 • SoC (defined as an antibody with anti C5 activity)
Pharmacokinetic assessments	• PK blood collection
Efficacy/PD assessments	• LDH • C3 fragment deposition • PNH-type red blood cells
Key safety assessments	• ECG • Blood Chemistry, hematology, urinalysis • Markers of thrombosis

	• Patient diary • Vital signs • Physical examination • Vaccinations • Incidence of transfusion • PRO • AE/SAE monitoring
Other assessments	• Biomarkers (in serum and plasma) • Commercially Confidential Information
Data analysis	The primary variable for assessing the effect of LNP023 (in addition to SoC) is the LDH value which is measured at multiple times during the study. A mixed model repeated measures (MMRM) analysis of variance model will be fitted to LDH levels over time. The model will include timepoint (as study day relative to start of study treatment) as a fixed effect, and baseline LDH as a fixed covariate. Baseline is defined to be the mean of the last 3 measurements prior to randomization. An unstructured variance-covariance matrix will be used. Results from this modelling will be presented as the estimated mean value of LDH at week 13 together with the 95% confidence interval. These results will also be presented graphically in a forest plot also showing published data from trials of eculizumab, as shown in Figure 11-1.
Key words	Complement, alternative pathway, paroxysmal nocturnal hemoglobinuria, hemolysis

1 Introduction

1.1 Background

Paroxysmal nocturnal hemoglobinuria (PNH) is a life threatening condition caused by a somatic mutation in hematopoietic stem cells leading to loss of cell surface complement regulatory proteins (CD55 & CD59) on all progeny cells including red blood cells (RBCs).

Without the glycophosphatidylinositol (GPI) anchor, CD59 is less expressed on the cell surface hence allowing for C5b-9 formation and erythrocyte lysis in process called intravascular hemolysis (Brodsky 2014). C3-coated erythrocytes can also undergo complement-mediated destruction by reticuloendothelial macrophages in the liver and spleen (opsonophagocytosis). In healthy subjects, this extravascular hemolysis is blocked by CD55, which prevents assembly of the C3 and C5 convertases on the cell surface and hence blocks C3 deposition of the cells.

Hemolysis in PNH is mainly due to complement-dependent intravascular hemolysis, which normally is blocked by CD59 (protectin) preventing the final stage of complement assembly. Without the GPI anchor, CD59 is less expressed on the cell surface hence allowing for MAC formation and erythrocyte lysis (Brodsky 2014). In untreated PNH patients, the anemia is dominated by the intravascular hemolysis (Subias Hidalgo et al 2017). In patients treated with eculizumab formation of the terminal complex is blocked, but there is accumulation of erythrocytes opsonized with C3 fragments, which makes them prone to undergo extravascular hemolysis (Hill et al 2010, Risitano et al 2009). In particular, C3dg fragments are strong signals for erythrophagocytosis (Lin et al 2015).

Indeed, patients with PNH treated with C5-blockade (eculizumab) often develop a Coombs-positive hemolytic anemia that is C3-positive, IgG-negative (Hill et al 2010, Risitano et al 2009). The ongoing hemolysis is a burden for the patients leading to severe anemia, iron deficiency, pain due to vasospasm and fatigue

Treatment of PNH with eculizumab, drastically reduce the intravascular hemolysis, but the patients show evidence of being suboptimally treated for their anemia. Thus, serum LDH levels remain elevated in most patients, 50% of patients are anemic and some require intermittent transfusions (Peffault de Latour et al 2015). PNH patients with extravascular hemolysis often display erythrocytes opsonized with C3, C3b, iC3b and C3dg, the direct Coombs-test is often positive, there is a high percentage of reticulocytes, bilirubin is elevated and the LDH levels are slightly elevated (Hill et al 2010, Risitano et al 2009). LNP023 blocks the AP and prevents C3 fragments from opsonizing the erythrocytes. Thereby, patients with PNH should experience less of extravascular and intravascular hemolysis (Risitano 2016, Subias Hidalgo et al 2017).

LNP023 is a novel oral small molecular weight compound, with first-in-class potential, that inhibits factor B (FB) of the alternative pathway (AP). Blockade of the AP with oral LNP023 has the potential to prevent both intra - and extravascular hemolysis and may, therefore, offer therapeutic superiority to the existing eculizumab Standard of Care (SoC) therapy that currently require intravenous (i.v.) infusions every second week.

1.2 Nonclinical data

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1.3 Clinical data

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1.4 Study purpose

The main purpose of this study is to evaluate the efficacy of LNP023 in patients with PNH, showing signs of active hemolysis despite treatment with SoC (defined as an antibody with anti C5 activity).

2 Objectives and endpoints

2.1 Primary objective(s)

Primary objective(s)	***Endpoints related to primary objective(s)***
• To assess the effect of LNP023 on the reduction of chronic hemolysis in PNH patients when administered in addition to SoC (monoclonal antibody with anti C5 activity)	• LDH level at study week 13

2.2 Secondary objective(s)

Secondary objective(s)	***Endpoints related to secondary objective(s)***
• To assess the safety and tolerability of LNP023 in patients with PNH when administered in addition to SoC (monoclonal antibody with anti C5 activity)	• All safety parameters including: blood chemistry, hematology, urinalysis, ECG evaluation, vital signs, adverse events, transfusions, PROs, patient diary
• To assess the effect of LNP023 on markers of intra and extravascular hemolysis when administered in addition to SoC (monoclonal antibody with anti C5 activity)	• Total and free hemoglobin, reticulocytes, LDH, C3 fragment deposition, PNH-type red blood cells, haptoglobin, bilirubin, red blood cell count, freedom from transfusion
• To assess the plasma PK of LNP023 in PNH patients	• Non-compartmental PK parameters or LNP023 in plasma, including but not limited to Cmax, Tmax and AUC and Ctrough.

2.3 Exploratory objective(s)

Exploratory objective(s)	*Endpoints related to exploratory objective(s)*
• To explore mechanism of action and PK-PD relationship of LNP023 in PNH patients when administered in addition to SoC (monoclonal antibody with anti C5 activity)	• Biomarker assessments may include but are not limited to Wieslab Assay, CH50, Bb, sC5b-9 • Population PK and PD model parameters. Correlation analysis and/or PK-PD modelling of biomarkers using total and/or unbound drug levels, as determined by means of ex-vivo dialysis, may also be explored
• To evaluate if co-treatment with LNP023 results in sustainable increases in hemoglobin	• Change in total hemoglobin level from baseline
• To assess LNP023-induced changes in quality of life	• Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue
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• To assess the effect of LNP023 on markers associated with risk of thrombosis in PNH patients	• Assessments may include but are not limited to prothrombin time, partial prothrombin time, D-dimer

3 Investigational plan

3.1 Study design

This is a non-confirmatory, open label, multiple dose study in patients with PNH. Two cohorts will be included into the study.

For Cohort 1 (approximately 10 patients) this study includes:

- a screening period of up to 68 days,
- a baseline visit,
- Treatment Part 1: 13 weeks of treatment with 200 mg LNP023 b.i.d. administered orally in addition to SoC,
- Treatment Part 2: Treatment extension for approximately 2 to 3 years with the same treatment regimen as used in Part 1 in patients who benefit from LNP023 treatment in Part 1 (see Section 4.1). Note that patients can complete Part 2 any time after a minimal total duration of LNP023 treatment of 2 years (i.e., after V130) without being considered early discontinuations, for example, to transition to the roll-over extension program (REP),

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- an End of Study (EoS) visit 2 weeks after last LNP023 administration for patients not joining the REP; for patients joining the REP, the last treatment visit will become the EoS visit.
- a safety follow-up call conducted 30 days after last LNP023 administration on CLNP023X2201 study (applicable only for patients not joining the REP).

For Cohort 2 (approximately 5 patients) this study includes:

- a screening period of up to 68 days,
- a baseline visit,
- Treatment Part 1: Minimum of 2 weeks of treatment with CCI LNP023 b.i.d. administered orally in addition to SoC. Dose of study medication can be increased to 200 mg LNP023 b.i.d. at study day 15 or anytime later in the study if LDH is not within limit of normal or reduced by at least 60% as compared to baseline values,
- Treatment Part 2: Treatment extension for approximately 2 to 3 years with the same treatment regimen as used in Part 1 in patients who benefit from LNP023 treatment in Part 1 (see Section 4.1). For patients receiving CCI the dose may be escalated as described for Part 1. Note that patients can complete Part 2 any time after a minimal total duration of LNP023 treatment of 2 years (i.e., after V130) without being considered early discontinuations, for example, to transition to the roll-over extension program (REP),

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- an End of Study (EoS) visit 2 weeks after last LNP023 administration for patients not joining the REP; for patients joining the REP, the last treatment visit will become the EoS visit.
- a safety follow-up call conducted 30 days after last administration of study treatment (applicable only for patients not joining the REP).

For all patients:

- The baseline visit can be skipped if Screening and Day 1 visits are not more than 7 days apart (Figure 3-1). If possible, study visits should be aligned with SoC administration. On Day 1 and any other visits when both SoC and LNP023 are administered, LNP023 is administered prior to SoC. Adjustments of the SoC dose or regimen are not allowed for the first 6 months of the treatment with LNP023.
- The expected study duration is between approximately 2.5 and 3.5 years.

Up to 15 PNH patients treated with SoC (defined as an antibody with anti C5 activity) with signs of active hemolysis will be included in the study. The presence of hemolysis will be verified based on LDH values, as specified in the Section 4.1. Pre-SoC sample collection for the LDH measurement used for inclusion purpose should be taken at the same day as planned SoC administration. LDH medical history data can be taken into consideration for inclusion

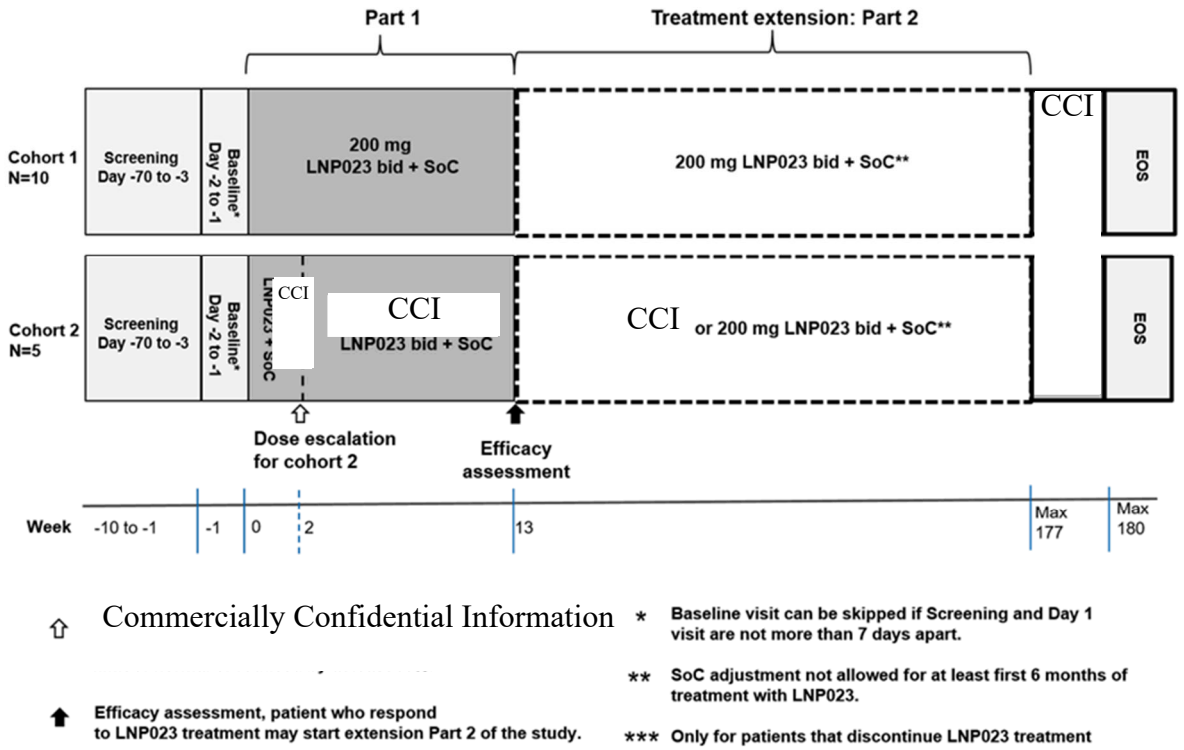
purpose. If medical history data is not available, the screening period may consist of up to 5 visits for LDH verification.

All patients need to complete vaccinations against *N. meningitidis*, *S. pneumoniae* and *H. influenzae* at least 4 weeks prior to starting LNP023 treatment. If LNP023 treatment has to start earlier than 4 weeks post vaccination, prophylactic antibiotic treatment must be initiated. After initial immunization, booster doses of the vaccinations should be administered according to the label of the vaccination used. The screening period may be extended to allow vaccination procedures to be completed. This is applicable for vaccinations only and all the other screening assessments should be performed within the period described in the assessment schedule.

Patients who benefit from LNP023 treatment in Part 1 of the study based on reduced hemolytic parameters (see inclusion criteria Section 4.1) can continue study treatment in extension Part 2.

Please refer to the Assessment schedule for details regarding assessments to be performed. Assessment schedule is identical for cohort 1 and cohort 2.

Figure 3-1 Study design



3.2 Rationale of study design

It has been demonstrated that over 40% of the PNH patients protected from intravascular hemolysis by an anti-C5 monoclonal antibody still show signs of active hemolysis (Peffault de Latour et al 2015). It is hypothesized that one important reason for elevated LDH levels in these patients is extravascular hemolysis mediated by accumulation of C3 fragment on red blood cells thereby leading to opsonization of erythrocytes. LNP023 specifically targets the alternative complement pathway and has been shown *in-vitro* to reduce the opsonization of the-

erythrocytes by C3 fragments (unpublished data). Therefore, to account for both intravascular and extravascular hemolysis and to build confidence of efficacy of LNP023, LNP023 will be administered in addition to any antibody with anti C5 activity that is currently available and used as SoC in this patient population. In addition, for patients already on C5 blockade, discontinuation of SoC in favor of LNP023 is not warranted at this time because the efficacy of LNP023 as a monotherapy in this indication is not confirmed yet. Modifications of the SoC regimen are allowed in study patients who respond to LNP023 after at least 6 months of concomitant treatment as per discretion of the Investigator after careful consideration of risk-benefit. As exposure to anti-complement activity of patients on SoC is known to reach sub-optimal levels towards the end of standard treatment interval of 2 weeks (increasing CH50 values, Peffault de Latour et al 2015), consequent changes in PD markers (such as LDH) can be observed in most patients on SoC when used at the label dose. It is expected that the addition of LNP023 to SoC will produce a constant complete complement blockade in these patients through the additional effect of factor B blockade. Therefore, overall hemolysis during the study is expected to decrease or disappear. We will investigate the relationship between alternative complement pathway blockade in the presence of varying exposures to SoC anti C5 activity and residual, extravascular hemolysis.

This is a non-placebo-controlled study since the absence of a placebo response in this patient population has been demonstrated (Hillmen et al 2006), and is expected given the nature of the primary outcome measure, which is a biochemical parameter. In addition considering available treatment options restricting PNH patients to placebo treatment would not be ethical.

To reduce the risk of infections, all the patients are either receiving prophylactic antibiotics or are vaccinated prior to first treatment with LNP023. The study will include an up to 68-day screening period to allow time to assure development of protective immunity. This long screening period also allows assessment of hemolysis based on the consistently elevated LDH levels. In addition, to reduce risk of infection, prophylactic antibiotics will be required for patients with any signs of infection as described in Section 3.1.

3.3 Rationale for dose/regimen, route of administration and duration of treatment

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3.4 Rationale for choice of comparator

Not applicable.

3.5 Rationale for choice of background therapy

To build confidence in efficacy of LNP023, it will be administered in addition to any antibody with anti C5 activity that is currently available and used as SoC in this patient population. Discontinuation of SoC in favor of LNP023 is not warranted at this time in Part 1 of the study because the efficacy of LNP023 in this indication is not confirmed yet, and the risk benefit evaluation is in favor of continuing C5 blockade until data of LNP023 in PNH becomes available. Change in the SoC treatment regimen will be allowed after minimum of 6 months of LNP023 treatment in Part 2 of the study that is open only to patients who respond to LNP023 treatment.

3.6 Purpose and timing of interim analyses/design adaptations

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3.7 Risks and benefits

3.7.1 General

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The risk to subjects in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, early stopping rules, periodic review of the safety data, and guidance for the investigators in the IB. The most relevant risks are described below. A complete list of toxicological findings is available in the Investigator Brochure Section 4.3.2.

Women of child bearing potential (WOCBP) 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 highly effective contraception requirements outlined in the Section 4.2 (Exclusion Criteria). If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

3.7.2 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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3.7.2.1 Infections

In this study, LNP023 is used to block the complement AP. Patients with mutations of factor B (FB) are generally 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).

Translational research has shown that the serological response to meningococcal infection is maintained during AP blockade, but that it is markedly reduced after blockade of the CP with C5-blockers like eculizumab (Konar et al 2016). 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 pneumococcal vaccines (McFetridge et al 2015, Bryant et al 2015).

Complement is important to trigger a serological response. Hence, the serological response to certain vaccinations is most likely blunted during active LNP023 treatment. Thus, important vaccinations should be performed prior to initiation of LNP023. Importantly, no live vaccines should be given to individuals during LNP023 treatment.

During the one-month run in phase, vaccination will be done according to local regulation and practice at least four weeks prior to the first dose to effectively increase the serological titers and reduce the risk for the individual in the unlikely event of bacterial infection with *N. meningitides, S. pneumoniae* or *H. influenzae*. The vaccines and the vaccination procedures recommended vary between countries and the details are therefore described in the SOM.

Patients will be closely monitored for signs and symptoms of infection. Patients will be instructed to contact the investigator if they suspect infection/experience potential symptoms of infection between visits (please refer to Section 3.7.4). The investigator will employ clinical judgement to determine an appropriate course of treatment and report infections as an AE. If symptoms of severe bacterial infections are reported, LNP023 treatment will be interrupted, bacterial cultures taken, and treatment with appropriate antibiotics immediately initiated.

With the prophylactic antibiotics, vaccinations and close monitoring described above, the risk for serious infection during LNP023 treatment is considered to be low.

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3.7.3 Blood sample volumes

Total maximum blood volume collected during this study will be 1400 mL:

- A maximum of 500 mL of blood is planned to be collected over a period of approximately 15 weeks from each patient in Part 1 of the study.
- Additional approximately 900 mL will be collected from patients participating in Part 2 of the study during approximately 3 years of treatment extension. In case patients finish the study after approximately 2 years of treatment, the additional blood volume collected in Part 2 will be approximately 700 mL.

Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the Assessment schedule Section 8.1.

A summary of the blood log is provided in the Site Operations Manual. Complete instructions for all sample collections, processing, storage and shipment information are available in the SOM and central Laboratory Manual.

See Section 8.9 regarding the potential use of residual samples.

3.7.4 Risk mitigation strategy

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All study patients will be clinically managed as if in severe neutropenia regardless of their actual neutrophils count. Specifically, the patients and treating staff need to be instructed to be vigilant for any clinical signs of infections (e.g. malaise, chills, fever, bone pain) and to measure the body temperature daily in Part 1 and at minimum at time of physical symptoms in Part 2 of the study until one week post last LNP023 treatment. Patients will be instructed to contact the study investigator immediately in case of suspicion of infection or elevated body temperature (>38.3°C by oral or tympanic method) for a phone consultation.

In case of a suspected infection, patients should either be admitted for emergency evaluation or empirically treated with an oral fluoroquinolone plus amoxicillin/clavulanate (or plus clindamycin if penicillin allergic), unless fluoroquinolone prophylaxis was used before fever developed (please refer to guidance provided in Flowers et al 2013, (Vol 31; p799, recommendation B4).

In order to mitigate the risk of the hemolytic events after LNP023 treatment discontinuation, 2 weeks of the LNP023 taper down period was implemented for patients discontinuing LNP023 treatment. In addition, the guidance was added on how to monitor the patients after study treatment discontinuation.

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, ECGs, clinical laboratory evaluations (hematology, blood chemistry and urinalysis), and AEs as outlined in the Assessment schedule. 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.

3.7.5 Rationale for Public Health Emergency mitigation procedures

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

4 Population

Study inclusion/exclusion criteria

Approximately 15 PNH patients with signs of active hemolysis will be included in the study.

4.1 Inclusion criteria

Study inclusion/exclusion criteria eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female patients between the age of 18-80 (inclusive) at baseline with a diagnosis of PNH based on documented clone size of ≥10% by RBCs and/or granulocytes, measured by GPI-deficiency on flow cytometry (screening or medical history data acceptable).
3. For Cohort 1 only: LDH values ≥1.5x upper limit of the normal range for at least 3 pre-SoC dosing measurements taken in relation to 3 different SoC dosing dates over a maximum of 10 weeks prior to Day 1 (screening, baseline or medical history data acceptable). All other screening pre-SoC LDH values have to be > 1x upper limit of normal range (for pre-SoC samples collected at the same day as SoC administration).
4. For Cohort 2: LDH values ≥1.25x upper limit of the normal range for at least 3 pre-SoC dosing measurements taken in relation to 3 different SoC dosing dates over a maximum of 10 weeks prior to Day 1 (screening, baseline or medical history data acceptable). All other screening pre-SoC LDH values have to be > 1x upper limit of normal range (for pre-SoC samples collected at the same day as SoC administration).
5. For Cohort 2 only: Hemoglobin level <10.5 g/dL at Baseline.
6. PNH patients on stable regimen of standard of care complement blockade (monoclonal antibody with anti C5 activity) for at least 3 months prior to first treatment with LNP023.
7. Previous vaccination against Neisseria meningitidis types A, C, Y and W-135 is required at least 4 weeks prior to first dosing with LNP023.Vaccination against N. meningitidis type B should be conducted if available and acceptable by local regulations, at least 4 weeks prior to first dosing with LNP023. If LNP023 treatment has to start earlier than 4 weeks post vaccination, prophylactic antibiotic treatment must be initiated.
8. Previous vaccination for the prevention of S. pneumoniae and H. influenzae at least 4 weeks prior to first dosing with LNP023. If LNP023 treatment has to start earlier than 4 weeks post vaccination, prophylactic antibiotic treatment must be initiated.
9. Able to communicate well with the investigator, to understand and comply with the requirements of the study.
10. For Part 2 of the study patients who as per judgment of Investigator benefit from LNP023 treatment based on reduced hemolytic parameters as compared to Screening and Baseline.

4.2 Exclusion criteria

Study inclusion/exclusion criteria fulfilling any of the following criteria are not eligible for inclusion in this study:

1. Participation in any other investigational drug trial or use of other investigational drugs at the time of enrollment, or within 5 elimination half-lives of enrollment, or within 30 days, whichever is longer; or longer if required by local regulations
2. Known or suspected hereditary complement deficiency at screening
3. History of hematopoietic stem cell transplantation as verified both at screening and at baseline (unless baseline was skipped)
4. Patients with laboratory evidence of bone marrow failure (reticulocytes $<60x10^9$/l, or platelets $<30x10^9$/l, or neutrophils $<1x10^9$/l) as verified both at screening and at baseline (unless baseline was skipped)
5. A positive HIV, Hepatitis B (HBV) or Hepatitis C (HCV) test result at screening
6. Presence or suspicion (based on judgment of the investigator) of active infection within 2 weeks prior to first dose of LNP023, or history of severe recurrent bacterial infections
7. History of recurrent meningitis, history of meningococcal infections despite vaccination as verified both at screening and at baseline (unless baseline was skipped)
8. Patients on the immunosuppressive agents such as but not limited to cyclosporine, MMF, tacrolimus, cyclophosphamide, methotrexate less than 8 weeks prior to first treatment with LNP023 unless on a stable regimen for at least 3 months prior to first LNP023 dose.
9. Systemic corticosteroids administered at the dose of $\geq$ 10 mg per day prednisone equivalent within less than 4 weeks prior to first treatment with LNP023
10. Severe concurrent co-morbidities, e.g. patients with severe kidney disease (dialysis), advanced cardiac disease (NYHA class IV), severe pulmonary arterial hypertension (WHO class IV), unstable thrombotic event not amenable to active treatment as judged by the investigator both at screening and at baseline (unless baseline was skipped)
11. Any medical condition deemed likely to interfere with the patient's participation in the study, or likely to cause serious adverse events during the study
12. Female patients who are pregnant or breastfeeding, or intending to conceive during the course of the study
13. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception from first dosing with LNP023 until EOS. **Highly effective contraception methods include:**

- Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.

- Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

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

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

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

Additional patients might be enrolled to replace patients who discontinue the study or treatment for reasons other than safety or lack of efficacy.

The investigator must ensure that all patients being considered for the study meet the eligibility criteria. No additional criteria should be applied by the investigator, in order that the study population will be representative of all eligible patients.

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

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

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

5 Restrictions for Study Subjects

For the duration of the study, the subjects should be informed and reminded of the restrictions outlined in this section:

- to use contraception as specified in below Section 5.1.
- to monitor body temperature and to contact the investigator immediately in case of suspicion of infection or elevated body temperature (>38.3°C by oral or tympanic method)
- to record any non-compliance in LNP023 intake in a dosing diary

5.1 Contraception requirements

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 requirement outlined in the Section 4.2 (Exclusion Criteria). If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

Male subjects should be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information. Please refer to Section 4.2 (Exclusion criteria) for details of contraception requirements for the study.

5.2 Prohibited treatment

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

Preclinical studies have shown that systemic disposition of LNP023 is likely cleared to be primarily mediated by metabolism clearance, in particular by the CYP450 family (primarily CYP2C8) as well as by direct glucuronidation. In addition, some minor contribution from direct renal and intestinal excretion is anticipated, and a contribution of OATP in hepatic uptake of LNP023 cannot be ruled out.

While drugs that interact with individual disposition pathways of LNP023 are unlikely to lead to a major increase in AUC for LNP023, co-administered drugs that inhibit multiple disposition mechanisms of LNP023 (e.g., Gemfibrozil) should be avoided.

Most importantly, LNP023 at the highest dose of 200 mg, may have an inhibitory effect on intestinal P-gp which could lead to an 2-4 fold increase in AUC of sensitive substrates. Therefore, it is recommended to use P-gp substrate with a narrow therapeutic index with caution and in a staggered dosing paradigm (victim drug such as cyclosporine, tacrolimus at least 3 hours after administration of LNP023). The investigator should consult Novartis for advice as needed.

Table 5-1 Prohibited medication

Medication	Prohibited period	Action to be taken
Immunosuppressive agents such as but not limited to cyclosporine, MMF, tacrolimus, cyclophosphamide, methotrexate unless on a stable regimen for at least 3 months before study Day 1	8 weeks before first LNP023 dose until EOS	To discontinue study treatment
Systemic corticosteroids	4 weeks before first LNP023 dose until EOS	To discontinue prohibited concomitant medication
Live vaccinations	4 weeks before first LNP023 dose until EOS	To discontinue study treatment
Gemfibrozil (PK interaction expected)	48h before first LNP023 dose until EOS	To discontinue study treatment
Strong CYP2C8 inhibitors (e.g., clopidogrel)	48h before first LNP023 dose until EOS	To discontinue prohibited concomitant medication
SoC dose or regimen* adjustments during first 6 months of LNP023 treatment	From Day 1 until Day 180	Decision to continue treatment with study medication: to by decided on the case by case basis

*Window of +/-2 days acceptable

5.3 Dietary restrictions and smoking

Not applicable.

5.4 Other restrictions

Not applicable.

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 treatment and control drug(s)

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6.1.2 Bio-batch retention samples

Not applicable.

6.1.3 Additional study treatment

No additional treatment beyond investigational drug and SoC are included in this trial.

6.1.3.1 Standard of Care

Standard of Care (SoC) is defined as a monoclonal antibody with anti C5 activity. As per Section 4.1, patients should be on stable SoC regimen for at least 3 months prior to first treatment with LNP023. If possible, study visits need to be aligned with SoC administration. On Day 1 and any other visits when both SoC and LNP023 are administered, LNP023 is administered prior to SoC. Adjustment of the SoC dose or regimen is not allowed during the first 6 months of the study. However, for stable patients without signs of active hemolysis who are at least for 6 months in the trial and having received continued concomitant treatment with LNP023 and eculizumab at a dose level of at least 900 mg IV q2w, the dose of eculizumab might be adjusted as per the investigator's discretion (e.g., a dose of 1'200 mg q2w might be reduced to 900 mg q2w).

Time and dose of SoC administered will be recorded in CRF. SoC is to be procured and administered by the site locally.

6.2 Treatment arms

Cohort 1: study patients will receive 200 mg of LNP023 twice per day (b.i.d.) in Part 1 and Part 2 of the study.

Cohort 2: study patients will receive CCI of LNP023 twice per day (b.i.d.) for at least 2 weeks. Dose of study medication can be increased to CCI LNP023 b.i.d. at study day 15 or anytime later in the study depending on the LDH level (Section 3.1).

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6.3 Treatment assignment and randomization

This is a non-randomized open-label study. Patient screening number (generated as described in the Site Operation Manual) will serve as each patient's identifier.

6.4 Treatment blinding

Not applicable.

6.5 Treating the subject

LNP023 will be administered orally at the patients' home or at the study center. On Day 1 and any other visits when both SoC and LNP023 are administered, LNP023 is administered prior to SoC.

As per Section 3.7.5, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of IMP directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. In this case, regular phone calls or virtual contacts (frequency as per planned visit) will occur between the site and the participant for instructional purposes, safety monitoring, investigation of any adverse events, ensuring participants continue to benefit from treatment, and discussion of the participant's health status until the participants can resume visits at the study site.

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

6.6 Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments that are not part of the study design and/or interruptions are not permitted.

6.7 Emergency breaking of assigned treatment code

Not applicable.

6.8 Treatment exposure and compliance

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects treated with LNP023, as detailed in Section 8.7.

6.9 Recommended treatment of adverse events

All study patients will be clinically managed as if in severe neutropenia regardless of their actual neutrophils counts. Specifically, the patients and treating staff need to be instructed to be vigilant for any clinical signs of infections (e.g. malaise, chills, fever, bone pain) and to measure the body temperature starting from first LNP023 administration until end of study. Patients will be instructed to contact the investigator immediately in case of suspicion of infection or elevated body temperature (>38.3°C by oral or tympanic method) for a phone directed triage.

In case of a suspected infection, patients should either be admitted for emergency evaluation or empirically treated with an oral fluoroquinolone plus amoxicillin/clavulanate (or plus clindamycin if penicillin allergic), unless fluoroquinolone prophylaxis was used before fever developed (please refer to guidance provided in Flowers et al 2013.

Please refer to Section 7.2 for guidance regarding treatment of AEs related with LNP023 discontinuation.

6.10 Rescue medication

Not applicable.

6.11 Concomitant treatment

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 prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

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 Novartis before including the patient in the study or, if the subject is already enrolled, to determine if the subject should continue participation in the study.

7 Study completion and discontinuation

7.1 Study completion and post-study treatment

Each patient will be required to complete the study in its entirety. Patients benefiting from LNP023 treatment will have the option to join the REP after a minimum of two years of treatment with LNP023. The end of treatment (EoT) visit will become the EoS visit for patients joining REP.

Study completion is defined as when the last patient completes the Study Completion 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.

All randomized and/or treated subjects, who are not joining the REP study, should have a safety follow-up call conducted 30 days after last administration of study treatment. All SAEs reported during this time period must be reported as described in Section 9.2. Documentation of attempts to contact the patients should be recorded in the source documentation at the sites.

7.2 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, the investigator, or sponsor.

Study treatment must be discontinued under the following circumstances:

- Patient decision - patient may choose to discontinue study treatment for any reason at any time.
- The investigator believes that continuation would negatively impact the safety of the subject or the risk/benefit ratio of trial participation.
- Any protocol deviation that results in a significant risk to the patient's safety.
- Pregnancy (see Section 8.6 (Safety) and Section 9.5 (Pregnancy reporting))
- Use of prohibited treatment as outlined in Table 5-1.

If discontinuation of study treatment occurs, investigator must determine the primary reason for the subject'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 (see Section 7.3, Withdrawal of Informed Consent). Where possible, they should return for EOS visit within 14 days after last study medication administration. If they fail to return for EOS visit for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in Section 7.4 (Lost to follow-up). This contact should preferably be done according to the study visit schedule.

If any patient discontinues study or study treatment with LNP023 they should be closely monitored for signs and symptoms of hemolysis. If possible, two weeks taper down is recommended for the patients who discontinue LNP023 treatment.

In case of the LNP023 treatment discontinuation parameters below are suggested to be closely monitored:

- greater than 25% absolute decrease in PNH clone size (in the absence of dilution due to transfusion) in one week or less;
- increase in LDH level;
- an hemoglobin level of < 8 g/dL or a decrease of > 4 g/dL in one week or less;
- angina pectoris;
- change in mental status;
- a 50% increase in serum creatinine level; or
- thrombosis.

If serious hemolysis occurs after LNP023 discontinuation, the following procedures/treatments should be considered by the investigator:

- blood transfusion (packed RBC), or exchange transfusion if the PNH RBC are > 50% of the total RBCs by flow cytometry;
- anticoagulation; corticosteroids; or
- other rescue medication.

7.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a subject:

- Does not want to further participate in the study, 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.

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

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

7.4 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should 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 cannot be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

7.5 Study stopping rules

Overall study stopping rules:

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 or more fatal or life-threatening SAE that is considered by the Investigator as potentially related to LNP023
- Two or more SAEs that are considered by the Investigator as potentially related to LNP023;
- At least 2 or more patients experience a similar AE which was assessed as severe in intensity, and are considered as potentially related to LNP023;
- The Sponsor or DMC considers that the number and/or severity of AEs, abnormal safety monitoring tests or abnormal laboratory findings justify putting the study on hold.

The study may resume following the safety review, if the Investigator, DMC and Sponsor agree it is safe to proceed.

In case of SAEs that signal safety risks that might directly affect other individuals that are still on treatment the safety lead will conduct a risk benefit assessment and decide whether to continue dosing in the unaffected individuals or not.

7.6 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. Should this be necessary, subjects must be seen as soon as possible and treated as a prematurely discontinued 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 will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Procedures and assessments

8.1 Assessment schedule

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. Please refer to Section 7.2 for guidance regarding discontinuation of study treatment.

As per Section 3.7.5, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ home nursing staff to the participant ´ s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

Table 8-1 Assessment Schedule

Epoch	Screening		Treatment																				
Visit Name	Screening	Baseline[2]	Treatment part 1																				
Visit Numbers[1]	1	2	101						102	103	104	105	106						107	108	109	110	111	112
Days	-70 to -3	-2 to -1	1						2	8 ±1	15 ±1	22 ±1	29 ±1						36 ±1	43 ±1	57 ±1	71 ±2	85 ±2	92 [11] ±2
week			1								2	3	4						5	6	8	10	12	13
Time (post-dose)	-	-	pre-dose	0.25h	1h	2h	4h	6h	-	-	-	-	pre-dose	0.25h	1h	2h	4h	6h	-	-	-	-	-	-
Informed consent	X																							
Medical history/current medical conditions	X																							
Vaccinations	X																							
Hepatitis and HIV Screen	S																							
Demography	X																							
Pregnancy[3]	S	S											S									S		S
Study drug administration[4]			X																					
Physical Examination[5]	X	X	X						X	X	X	X	X						X	X	X	X	X	X
Pulse rate[5]	X	X	X						X	X	X		X						X	X	X	X	X	X
Blood Pressure[5]	X	X	X						X	X	X		X						X	X	X	X	X	X
Body Temperature[5]	X	X	X						X	X	X	X	X						X	X	X	X	X	X
Body Height	X																							
Body Weight	X	X	X								X		X							X		X		X
Electrocardiogram (ECG)[5]	X	X	X						X	X	X		X							X		X		X
Hematology[5]	X	X	X						X	X	X	X	X						X	X	X	X	X	X
Clinical Chemistry[5,9]	X	X	X						X	X	X	X	X						X	X	X	X	X	X
Urinalysis[5]	X	X	X						X	X	X	X	X						X	X	X	X	X	X
Markers of thrombosis[6]	X	X	X						X	X	X	X	X						X	X	X	X	X	X
PK blood collection[5]			X	X	X	X	X	X	X	X	X		X	X	X	X	X	X			X			X
PNH-Clone size	X																							
Exploratory Biomarkers in Serum[6]		X	X			X		X		X	X	X	X								X			X
Exploratory Biomarkers in Plasma[6]		X	X			X		X		X	X	X	X								X			X
C3 deposition, PNH-type red blood cells[6]		X	X			X		X		X		X	X								X			X
Commercially Confidential Information																								
Patient reported outcomes	X	X	X						X	X	X	X	X								X			X
Patient diary[7]			X										X											
Incidence of transfusion[10]	X																							
Adverse Events	X																							
Concomitant medications	X																							
Comments	X																							
Study completion information																								

Epoch	Treatment																				
Visit Name	Treatment Part 2, 1st year																				
Visit Numbers[1]	113	114	115	116	117						118	119	120	121	122	123					
Days	113	127	141	155	169						197	225	253	281	309	337					
	±2	±2	±2	±2	±2						±2	±3	±3	±3	±3	±3					
week	16	18	20	22	24						28	32	36	40	44	48					
Time (post-dose)					pre-dose	0.25h	1h	2h	4h	6h						pre-dose	0.25h	1h	2h	4h	6h
Informed consent																					
Medical history/current medical conditions																					
Vaccinations																					
Hepatitis and HIV Screen																					
Demography																					
Pregnancy[3]	S		S		S						S	S	S	S	S	S					
Study drug administration[4]	X																				
Physical Examination[5]	X		X		X						X	X	X	X	X	X					
Pulse rate[5]	X		X		X						X	X	X	X	X	X					
Blood Pressure[5]	X		X		X						X	X	X	X	X	X					
Body Temperature[5]	X	X	X	X	X						X	X	X	X	X	X					
Body Height and weight																					
Electrocardiogram (ECG)[5]	X		X		X						X	X	X	X	X	X					
Hematology[5]	X	X	X	X	X						X	X	X	X	X	X					
Clinical Chemistry[5,9]	X	X	X	X	X						X	X	X	X	X	X					
Urinalysis[5]	X	X	X	X	X						X	X	X	X	X	X					
Markers of thrombosis[6]	X	X	X	X	X						X	X	X	X	X	X					
PK blood collection[5]					X	X	X	X	X	X						X	X	X	X	X	X
PNH-Clone size																					
Exploratory Biomarkers in Serum[6]	X		X		X								X			X					
Exploratory Biomarkers in Plasma[6]	X		X		X								X			X					
C3 deposition, PNH-type red blood cells[6]	X		X		X								X			X					
Patient reported outcomes	X		X		X								X			X					
Patient diary[7]	X																				
Incidence of transfusion[10]	X																				
Adverse Events	X																				
Concomitant medications	X																				
Comments	X																				
Study completion information																					

Epoch		Treatment										
Visit Name		Treatment Part 2, 2nd-3rd year								Taper down		EOS [13, 15]
year 2	Visit Numbers[1]	124	125	126	127	128	129	130 [14]	131			
	Days	393	449	505	561	617	673	729	785			
		±7	±7	±7	±7	±7	±7	±7	±7			
	week	56	64	72	80	88	96	104	112			
year 3	Visit Numbers[1]	132	133	134	135	136	137	138	139	201	202	199
	Days	841	897	953	1009	1065	1121	1177	1233 [12]	between 99 and 1240	between day 106 and 1247	between day 120 and 1261 (2 weeks after last LNP023 dose for patients not joining REP)
		±7	±7	±7	±7	±7	±7	±7	±28	±1	±1	±3
	week	120	128	136	144	152	160	168	176	between 14 and 177	between 15 and 178	17 or 180
Informed consent												
Medical history/current medical												
Vaccinations												
Hepatitis and HIV Screen												
Demography												
Pregnancy[3]		S	S	S	S	S	S	S	S			S
Study drug administration[4]		X										
Physical Examination[5]		X	X	X	X	X	X	X	X	X	X	X
Pulse rate[5]		X	X	X	X	X	X	X	X	X	X	X
Blood Pressure[5]		X	X	X	X	X	X	X	X	X	X	X
Body Temperature[5]		X	X	X	X	X	X	X	X	X	X	X
Body Height and weight												X
Electrocardiogram (ECG)[5]				X			X			X	X	X
Hematology[5]		X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry[5,9]		X	X	X	X	X	X	X	X	X	X	X
Urinalysis[5]		X	X	X	X	X	X	X	X	X	X	X
Markers of thrombosis[6]		X	X	X	X	X	X	X	X	X	X	X
PK blood collection[5]				X			X		X	X	X	
PNH clone size												
Exploratory Biomarkers in Serum[8]				X			X		X	X	X	X
Exploratory Biomarkers in Plasma[8]				X			X		X	X	X	X
C3 deposition, PNH-type red blood				X			X		X	X	X	X

Patient reported outcomes		X	X	X	X	X	X	X	X	X	X	X
Patient diary[7]		X										
Incidence of transfusion[10]		X										
Adverse Events		X										
Concomitant medications		X										
Comments		X										
Study completion information												X

[1] Visit structure given for internal programming purpose only

[2] Baseline visit can be skipped if Screening and Day 1 visit are not more than 7 days apart

[3] Serum pregnancy test required at screening, urine pregnancy test at further time points

[4] LNP023 to be administered b.i.d daily

[5] To be done pre-LNP023 dose if applicable

[6] Samples to be collected pre-LNP023 and pre-SoC dose if applicable

[7] Body temperature measurement and dose administration diary

[8] Commercially Confidential Information

[9] Including blood hormone levels

[10] The history of transfusions administered within one year before baseline and the number of transfusions while on treatment with LNP023 will be recorded.

[11] Commercially Confidential Information

[12]

[13] A safety follow-up call will be conducted 30 days after last administration of study treatment (for patients not joining REP)

[14] Minimal treatment duration for patients participating in Part 2

[15] EoT visit for patients joining REP will become EoS visits. All EoS assessments to be performed at EoT/EoS visit. Patients not joining REP should complete EoS visit 2 weeks after last LNP023 administration

S- kept as a source data only

8.2 Informed consent procedures

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

If applicable, in cases where the subject's representative 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 assent by personally signing and dating the written informed consent document or a separate assent form.

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

Novartis will provide to investigators a proposed informed consent form that complies with the ICHE6 GCP guideline and regulatory requirements and is considered appropriate for this study. The informed consent form will also include a section related to optional future research which will require a separate signature if the subject agrees to future research. The procedures set out in the main consent form concerning the storage, maintenance of privacy, and release of the data or specimens for the main study will also be adhered to for any future research. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). 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.

Ensure subjects are informed of the contraception requirements outlined in the Section 4.2 (Exclusion criteria) and in Section 5.1 (Contraception requirements).

Commercially Confidential Information

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

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

8.3 Subject screening

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

8.4 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects. Hepatitis and HIV tests will be performed for samples collected at screening. 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.

8.4.1 PNH clone size

PNH cells lack the surface proteins CD55 and CD59. If no historic data is available flow cytometry will be performed to confirm diagnosis of PNH based on documented clone size of ≥10% by RBCs and/or granulocytes, measured by GPI-deficiency. Data will be entered into the eCRF.

8.4.2 Demography

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.

8.4.3 Medical history/current medical conditions

Relevant medical history and current medical conditions will be recorded on the CRF until signature of the informed consent.

Where possible, diagnoses and not symptoms will be recorded.

Any event or change in the subject's condition or health status occurring *prior to* informed consent will be reported in the Relevant medical history / Current medical conditions section of the CRF.

8.4.4 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. See the Assessment schedule, for timing of the protocol required pregnancy testing; 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 9.5 for details on Reporting Pregnancy.

Assessments of Fertility

Refer to Section 4.2 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. 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.

In the absence of the above medical documentation, FSH testing is required of any female subject who states that they are of non-child bearing potential, regardless of reported reproductive/menopausal status at screening/baseline.

8.5 Efficacy / Pharmacodynamics

Efficacy in this study will be measured based on the clinical chemistry parameter lactate dehydrogenase (LDH),C3 fragment deposition and PNH-type red blood cells.

8.5.1 LDH

Serum LDH is a measure for intravascular hemolysis and is usually elevated in PNH patients. In order to help characterize disease status and progression, historical values of serum LDH prior to the informed consent signature (if available), may be recorded in the eCRF as part of the medical history assessment and to verify inclusion/exclusion criteria. The blockade of complement mediated lysis of erythrocytes is expected to result in reduction of serum LDH levels. LDH will be determined in serum by a validated assay. Detailed methodological description of the assay will be included in the bioanalytical data report. Please refer to Assessment Schedule for timepoints when clinical chemistry is done. All the LDH values collected during the screening should be recorded in the CRF. If available as a part of the patients' medical history, at least the 5 most recent LDH values recorded prior to screening visit should be recorded in the CRF in order to characterize the pre-treatment LDH profile over time.

8.5.2 C3 fragment deposition and PNH-type red blood cells

In patients treated with anti C5 antibody there is an accumulation of CD59 negative cells positive for C3 fragments. These cells are prone to phagocytosis causing extravascular hemolysis.

Level of C3 deposition on red blood cells, as well as the proportion of PNH-type red blood cells will be quantified. Whole blood samples will be collected at the clinical sites at the time point described in the Assessment schedule and samples will be shipped to the analytical lab as described in a Site Operations Manual / central laboratory manual. Detailed descriptions of the assays will be included in the bioanalytical data reports.

8.6 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the Site Operations Manual, with the Assessment schedule Section 8.1 detailing when each assessment is to be performed.

8.6.1 Electrocardiogram (ECG)

Full details of all procedures relating to the ECG collection and reporting are contained in the ECG laboratory technical manual provided by ECG central reader.

In the event that a clinically significant ECG abnormality is identified at the site (e.g. severe arrhythmia, conduction abnormality of QTcF > 500 ms), then a copy of the assessment is sent to the core laboratory for expedited review if applicable, and the ECG is repeated to confirm the diagnosis. If the subject is hemodynamically compromised, the investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example cardioversion).

These parameters should be recorded: PR interval, QRS duration, heart rate, RR interval, QT interval, QTc

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

Clinically significant abnormalities must be reported in the AE CRF.

8.6.2 Clinical Chemistry

Sodium, potassium, creatinine, urea, uric acid, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, CRP, LDH, GGT, AST, ALT, aPTT, PT/INR, CK, glucose, total cholesterol, and triglycerides data will be collected.

- Bilirubin: Bilirubin is released during hemolysis and is frequently increased in PNH patients. Serum levels will be determined using standard procedures. If the total bilirubin concentration is increased above 3 times above the baseline value, direct and indirect reacting bilirubin should be differentiated.
- Ferritin: Ferritin levels have been reported to increase during treatment with eculizumab, and are a measure for iron overload. Serum levels will be determined using standard procedures.
- In the absence of the medical documentation specified in the Section 8.4.4, FSH testing is required of any female subject who states that they are of non-child bearing potential, regardless of reported reproductive/menopausal status at screening or baseline.

8.6.2.1 Blood hormone levels

The hormones analyzed are: T3, T4, TSH, reversed T3, testosterone, FSH, LH and DTH. Blood hormone levels are measured at every visit when blood chemistry is done.

8.6.3 Hematology

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

8.6.4 Markers of thrombosis

Prothrombin time, partial prothrombin time, D-dimer will be measured.

8.6.5 Urinalysis

Dipstick measurements for protein, blood, and WBC/leukocytes will be performed.

If dipstick measurement results are positive (abnormal), results will be captured in the CRF. Microscopy must be assessed following an abnormal dipstick test with results captured in the CRF.

8.6.6 Patient diary

Patient diaries will be used to record any elevation of body temperature >38.3°C and also record any missed administration of LNP023.

Body temperature should be measured daily in Part 1 of the study and at minimum at the time of physical symptoms in Part 2 of the study. The investigator shall review the diary at every visit. As per the investigator's decision, any clinically significant findings will be recorded in the CRF AE page. Patients will be instructed to contact the study physician immediately in case of suspicion of infection or elevated body temperature (>38.3°C by oral or tympanic method) for a phone directed consultation. In case of a suspected infection, patients should either be admitted for emergency evaluation or empirically treated with an oral fluoroquinolone plus amoxicillin/clavulanate (or plus clindamycin if penicillin allergic), unless fluoroquinolone prophylaxis was used before fever developed (please refer to guidance provided in Flowers et al 2013).

In case of clinically significant abnormal values, it will be recorded in the AE CRF page (as per judgement of the investigator).

8.6.7 Vital signs and body measurements

- Height
- Body weight
- Body mass index (BMI) will be calculated (Body weight (kg) / [Height (m)]^2)
- Pulse rate
- Blood pressure
- Body temperature

8.6.8 Physical Examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed. Information about all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to informed consent are included in the Relevant Medical History CRF. Significant findings observed after informed consent signature which meet the definition of an Adverse Event must be appropriately recorded on the Adverse Event CRF.

8.6.9 Vaccinations

Vaccination will be performed according to local recommendations for patients with complement deficiencies, if prior vaccination cannot be confirmed. The choice of vaccine(s) should take into account the serotypes prevalent in the geographic areas in which study patients will be enrolled.

The vaccinations against N. meningitidis, S. pneumoniae, and H. influenzae should be administered at least 4 weeks prior to starting LNP023 treatment. If LNP023 treatment has to start earlier than 4 weeks post vaccination, prophylactic antibiotic treatment must be initiated.

Re-vaccinations during LNP023 therapy should be applied as per label of used vaccinations.

8.6.10 Incidence of transfusion

The number of blood transfusions (and number of units transfused) will be counted and recorded in the eCRF. The history of transfusions administered within one year before baseline and the number of transfusions while on treatment with LNP023 will be recorded.

8.6.11 Patient reported outcomes

The validated Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) will be administered to assess fatigue of PNH patients. FACIT will be completed by study patients at the timepoints specified in the Assessment schedule.

8.7 Pharmacokinetics

PK samples will be collected at the time points defined in the Assessment schedule.

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

Plasma PK samples remaining after completion of the determination of parent may be used for exploratory purposes to further characterize the PK or PK/PD of LNP023. This analysis may include assessment of e.g., metabolite profiling, plasma levels of Fb, or other bioanalytical purposes (e.g. stability assessment). Given the exploratory nature of the work, the analytical method used for those assessments will not be validated. As such the results from this exploratory analysis will not be included in the clinical study report.

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 method(s) with Phoenix WinNonlin (Version 6.2 or higher):

Plasma: Cmax, Tmax, AUCtau after the first dose at Day 1

Plasma: Cmax,ss, Tmax,ss, AUCtau,ss, Cmin,ss, , T1/2 at Day 29. In addition Racc will also be determined. Other pharmacokinetic parameters as appropriate. To denote parameters determined at steady state “ss” will be used.

The linear trapezoidal rule will be used for AUC calculation. Due to the limited PK sampling regression analysis of the terminal plasma elimination phase for the determination of T1/2 will likely not be possible. If the adjusted R2 value of the regression analysis of the terminal phase is less than 0.75, no values will be reported for T1/2 and AUCinf.

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

8.8 Other assessments

8.8.1 Exploratory biomarkers in serum

8.8.1.1 Alternative complement pathway activity (Wieslab assay)

The terminal complex activity of the complement system is expected to be inhibited by LNP023 through inhibiting the alternative complement pathway. The degree of inhibition will be assessed using the Wieslab assay which is based on the in vitro formation of the C5b-9 complex, triggered by alternative pathway activation.

A detailed description of the method used to quantify the complement activity will be included in the bioanalytical data report.

8.8.1.2 Classical complement pathway activity (CH50 assay)

Standard of care is expected to inhibit the terminal complex activity of the complement system. The degree of inhibition with SoC only (baseline) and with both SoC and LNP023 will be assessed using the CH50 assay which is based on the in vitro formation of the C5b-9 complex, triggered by classical pathway activation.

CH50 will be assessed using existing serum samples from the Wieslab assay. A detailed description of the method used to quantify the complement activity will be included in the bioanalytical data report.

8.8.2 Exploratory biomarkers in plasma

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

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

The list may be changed or expanded further as it is recognized that more relevant or novel biomarkers may be discovered during the conduct of the study. Additional biomarkers related to the disease or patient's treatment may also be measured from leftover samples. Detailed descriptions of the assays will be included in the bioanalytical data reports.

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8.9 Use of residual biological samples

Residual blood and urine samples may be used for another protocol specified endpoint.

Any residual samples remaining after the protocol-defined analysis has been performed may be used for additional exploratory analysis. This may include, but is not limited to, using residual samples for protein binding, metabolite profiling, biomarkers of transporters or metabolic enzyme activity (such as 4-beta-hydroxycholesterol levels) or other bioanalytical purposes (e.g. cross check between different sites and/or stability assessment). Given the exploratory nature of the work, the analytical method used for those assessments will not be validated. As such, the results from this exploratory analysis will not be included in the clinical study report.

9 Safety monitoring

9.1 Adverse events

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

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an adverse event irrespective if a clinical event has occurred. See Section 9.4 for an overview of the reporting requirements.

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 finding, laboratory test finding, or other assessments.

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 should 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 patients with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for liver and kidney related events are included in Appendix 1 and Appendix 2, respectively.

Adverse events should be recorded on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

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
   - Yes or
   - No
3. its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a SAE (see Section 9.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding investigational treatment.

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

- no action taken (e.g. further observation only)
- investigational treatment dosage increased/reduced
- investigational treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- hospitalization/prolonged hospitalization (see Section 9.2 for definition of SAE)

6. its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

Information about common side effects already known about the investigational drug can be found in the IB or will be communicated between IB updates in the form of Investigator Notifications. Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the investigational drug, the interventions required to treat it, and the outcome.

The investigator must also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

*Refer to the Section 9.2.2.1 for data capture methodology regarding AE collection for subjects that fail screening.

9.2 Serious adverse event reporting

9.2.1 Definition of SAE

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:

- is fatal or life-threatening
- 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 the start of study drug
- 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
- social reasons and respite care in the absence of any deterioration in the subject's general condition

- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention.

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

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 ICH-E2D Guideline 2003).

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. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to ICH-E2D Guideline 2003).

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

All AEs (serious and non-serious) are captured on the CRF; SAEs also require individual reporting to Novartis Chief Medical Office and Patient Safety (CMO & PS) as per Section 9.2.2.

9.2.2 SAE reporting

Screen Failures

Note the following requirement for 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 Novartis.

Treated Subjects

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent until 30 days after last dose must be reported to Novartis immediately, without undue delay, and under no circumstances later than within 24 hours of learning of its occurrence as described below. The 30 day safety follow up will be completed as a part of the REP for patients joining roll-over extension.

Any SAEs experienced after this period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

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 immediately, without undue delay, and under no circumstances later than 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.

Follow-up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable) and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

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 Chief Medical Office and Patient Safety (CMO& PS) Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

9.2.2.1 Reporting SAE for patients who fail screening

In the event a patient who fails screening reports an SAE, the following information should be captured in the CRF:

- Visit 1 date
- Demography
- Informed consent
- Study completion page for the screening epoch
- Withdrawal of Informed Consent (if applicable)
- Death page (only in case of death)
- Reason for screen failure (e.g. Screening Study Disposition page)

9.2.2.2 How to report Serious Adverse Events (SAEs)

Information about all SAEs (either initial or follow up information*)* is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to each specific component of study treatment, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department.

In addition, the Medical Lead should be immediately notified by email. The patient line of the email should be as follows:

"Re: Urgent - SAE reported: Study CLNP023X2201".

The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

9.3 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.

Please refer to Table 15-1-Appendix 1 for complete definitions of liver events.

Follow-up of liver events

Every liver event defined in Table 15-1-Appendix 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 15-2-Appendix 1.

- Repeating liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation within 48-72 hours.

These liver chemistry repeats should always be performed using the central laboratory, with the results provided via the standard electronic transfer. If results will not be available from the central laboratory within 24 hours, then the repeats can also be performed at a local laboratory to monitor the safety of the subject.

All follow-up information, and the procedures performed must be recorded on the appropriate CRFs. Refer to the Site Operations Manual for additional details.

9.4 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, patient/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.

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) CRF. Study treatment errors are only to be reported to Chief Medical Office and Patient Safety (CMO& PS) department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the adverse event (AE) CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to Novartis Chief Medical Office and Patient Safety (CMO& PS). As such, instances of misuse or abuse are also to be reported using the SAE form/CRF. Table 9-1 summarizes the reporting requirements.

Table 9-1 Guidance for capturing study treatment errors

Treatment error type	Document in Dose Administration (DAR) CRF	Document in AE CRF	Complete SAE form/CRF
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 Section 9.1 and Section 9.2, respectively.

9.5 Pregnancy reporting

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

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Chief Medical Office and Patient Safety (CMO& PS) Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

The study drug must be discontinued, though the subject may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

9.6 Early phase safety monitoring

The Investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

10 Data review and database management

10.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The 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 ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

Continuous remote monitoring of each site's data may be performed by Novartis or CRO working on behalf of Novartis. Additionally, a central analytics organization may analyze data and identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety 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.

10.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF) using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. 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 CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the Site Operations Manual and Assessment schedule Section 8.1 and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

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

10.3 Database management and quality control

Novartis staff or CRO working on behalf of Novartis review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to CRO working on behalf of Novartis who will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant 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.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

ECG readings will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis management.

10.4 Data Monitoring Committee

An external, independent Data Monitoring Committee (DMC) will be created to review study data. The DMC will review the available safety data after the first 5 patients have completed 4 weeks of LNP023 treatment, after all 10 patients have completed LNP023 treatment and after all study patients complete the treatment In case of any safety concerns identified during the study, additional DMC meetings will be scheduled. Further details will be provided in the DMC charter.

10.5 Adjudication Committee

Not required.

11 Data analysis

The analysis will be conducted on all subject data at the time each Part ends. All outputs described below will be produced for Part 1 and at the end of the study extended into Part 2. Where appropriate, outputs will be split by Part, but longitudinal plots, for example, will cover both Parts at the end of the study analysis.

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

11.1 Analysis sets

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

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

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

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

11.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by subject. Summary statistics will be provided.

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

11.3 Treatments

Data for study drug administration and any concomitant therapies will be listed by subject.

11.4 Analysis of the primary variable(s)

The primary objective of this study is to assess the effect of LNP023 on the reduction of chronic hemolysis, as assessed by LDH over time, in PNH patients when LNP023 is administered in addition to SoC (monoclonal antibody with anti C5 activity).

11.4.1 Primary Variable(s)

The primary variable is LDH level and it is measured over time with week 13 (end of Part 1) considered the primary timepoint.

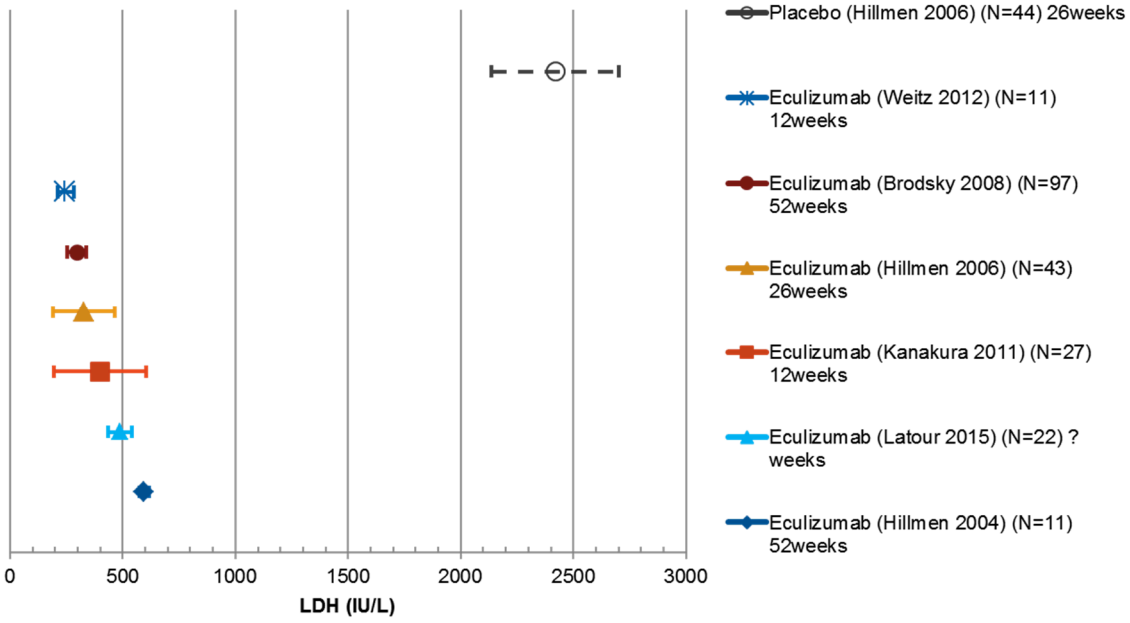
11.4.2 Statistical model, hypothesis, and method of analysis

The primary variable for assessing the effect of LNP023 (in addition to SoC) is the LDH value which is measured at multiple times during the study in both Parts.

A mixed model repeated measures (MMRM) analysis of variance model will be fitted to LDH levels over time in Part 1. The model will include timepoint (as study day relative to start of study treatment) as a fixed effect, and baseline LDH as a fixed covariate. Baseline is defined to be the mean of the last 3 measurements prior to randomization. An unstructured variance-covariance matrix will be used.

Results from this modelling will be presented as the estimated mean value of LDH at week 13 together with the 95% confidence interval. These results will also be presented graphically in a forest plot also showing published data from trials of eculizumab, as shown below in Figure 11-1. Two of the comparative studies are known to be at the same time point but all comparisons to this study's estimate will be useful given their similarity.

Figure 11-1 Forest plot of LDH final mean estimates at from 6 studies of various lengths



11.4.3 Handling of missing values/censoring/discontinuations

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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.

11.4.4 Sensitivity analyses

There is no obvious sensitivity analysis because with so few subjects, differences in results between different analyses are unlikely to be detected. However the effect of different ways of handling baseline LDH values, different variance-covariance structures and different fixed effect models could be examined to ensure robustness of results.

11.5 Analysis of secondary variable(s)

Secondary safety variables include blood chemistry, hematology, urinalysis, ECG evaluation, vital signs, adverse events, transfusions, and PROs. Secondary PK variables include total drug LNP023 non-compartmental PK parameters, including but not limited to Cmax and AUC and trough evaluation. Secondary PD variables as markers of disease activity include total and free hemoglobin, haptoglobin, reticulocytes, C3 fragment deposition, red blood cell count, and freedom from transfusion, as well as LDH values for patients in Part 2.

11.5.1 Efficacy / Pharmacodynamics

The continuous PD variables of total and free hemoglobin, LDH, haptoglobin, reticulocytes, C3 fragment deposition, PNH-type red blood cells and red blood cell count will be listed and plotted longitudinally by subject over both Parts. The number and timing of transfusions will be listed and each one shown on plots where relevant.

11.5.2 Safety

This study specifies blood chemistry, hematology, urinalysis, ECG evaluation, vital signs, adverse events, transfusions, and PROs as secondary objectives. Therefore continuous safety variables will also be plotted longitudinally as for LDH and PD variables, with events of interest such as transfusions also shown graphically. Otherwise the standard treatment of safety data is described below.

Vital signs

All vital signs data will be listed by subject and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by visit/time.

ECG evaluations

All ECG data will be listed by subject and visit/time, and abnormalities will be flagged. Summary statistics will be provided by visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by subject and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by visit/time.

Adverse events

All information obtained on adverse events will be displayed by subject and summarised overall.

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term. A subject with multiple adverse events within a body system is only counted once towards the total of this body system.

11.5.3 Pharmacokinetics

PK variables are total drug LNP023 non-compartmental PK parameters, including but not limited to Cmax, Tmax, AUC and trough evaluation.

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

A geometric mean will not be reported if the dataset includes zero values. Pharmacokinetic parameters will be calculated as described in Section 8.7 and will be listed by subject.

11.5.4 Pharmacokinetic / pharmacodynamic interactions

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A possible additive or synergistic PD interactions with the SoC is part of the study objective. For safety aspects of PK or PD interactions please refer to inclusion/exclusion criteria (Section 4).

11.5.5 Other assessments

Not applicable.

11.6 Analysis of exploratory variables

Any statistical analyses of exploratory endpoints beyond listings and longitudinal plots by subject will be described in the RAP.

11.6.1 Exploratory biomarkers

Biomarker assessments may include but are not limited to Wieslab Assay, CH50, Bb and sC5b-9.

All biomarker data will be listed by subject, and visit/time. Summary statistics will be provided by visit/time.

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11.6.3 Other Exploratory biomarkers

Change in total hemoglobin level from baseline to end of 13 weeks of LNP023 administration and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue are also exploratory endpoints, as well as prothrombin time, partial prothrombin time, and D-dimer.

11.7 Sample size calculation

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11.8 Power for analysis of key secondary variables

Not applicable.

11.9 Interim analyses

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12 Ethical considerations

12.1 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 Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 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 Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

For multi-center trials, a Coordinating Investigator will be selected by Novartis by the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

12.3 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

12.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed or overseen by Novartis Pharma Auditing and Compliance Quality Assurance (or CRO working on behalf of Novartis), a group 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 Novartis processes.

13 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 is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

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

13.1 Protocol Amendments

Any change to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation.

Amendments that are intended to eliminate an apparent immediate hazard to subjects 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, the reporting requirements identified in Section 9 (Safety Monitoring) must be followed and the Study Lead informed.

14 References

References are available upon request.

Alanee SR, McGee, L, Jackson D, et al (2007) Association of serotypes of Streptococcus pneumoniae with disease severity and outcome in adults: an international study. Clin Infect Dis; 45(1):46-51.

Brodsky RA (2014) Paroxysmal nocturnal hemoglobinuria. Blood; 2804-11.

Bryant KA, Frenck R, Gurtman A, et al (2015) Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine in adults 18-49 years of age, naive to 23-valent pneumococcal polysaccharide vaccine. Vaccine; 33(43):5854-60.

Flowers CR, Seidenfeld J, Bow EJ, et al (2013) Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol; 794-810.

Gossger N, Snape MD, Yu LM, et al (2012) Immunogenicity and tolerability of recombinant serogroup B meningococcal vaccine administered with or without routine infant vaccinations according to different immunization schedules: a randomized controlled trial. JAMA; 307(6):573-82.

Hill A, Rother RP, Arnold L, et al (2010) Eculizumab prevents intravascular hemolysis in patients with paroxysmal nocturnal hemoglobinuria and unmasks low-level extravascular hemolysis occurring through C3 opsonization. Haematologica; 95:567-573.

Hillmen P, Young NS, Schubert J, et al (2006) The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med; 1233-43.

ICH Harmonised Tripartite Guideline (2003). Post-approval safety data management: definitions and standards for expedited reporting E2D.

Keyserling H, Papa T Koranyi K, et al (2005) Safety, immunogenicity, and immune memory of a novel meningococcal (groups A, C, Y, and W-135) polysaccharide diphtheria toxoid conjugate vaccine (MCV-4) in healthy adolescents. Arch Pediatr Adolesc Med; 159(10): 907-13.

Konar M, Lujan E, and Granoff D (2016) Effect of Complement Inhibition By Anti-C5 (Eculizumab) or a Small Molecule Inhibitor of Factor D (ACH-4471) on Survival of Meningococci in Blood from Vaccinated Adults. In Paper Presented to the American Society of Hematology 58th Annual meeting, San Diego, CA.

Lin Z, Schmidt CQ, Koutsogiannaki S, et al (2015) Complement C3dg-mediated erythrophagocytosis: implications for paroxysmal nocturnal hemoglobinuria. Blood; 126(7):891-4. doi: 10.1182/blood-2015-02-625871.

MacNeil JR, Cohn AC, Farley M, et al (2011) Current epidemiology and trends in invasive Haemophilus influenzae disease--United States, 1989-2008. Clin Infect Dis; 53(12):1230-6.

McFetridge R, Meulen AS, Folkerth SD, et al (2015) Safety, tolerability, and immunogenicity of 15-valent pneumococcal conjugate vaccine in healthy adults. Vaccine; 33(24):2793-9.

Peffault de Latour R, Fremeaux-Bacchi V, Porcher R, et al (2015) Assessing complement blockade in patients with paroxysmal nocturnal hemoglobinuria receiving eculizumab. Blood; 775-83.

Risitano AM, Notaro R, Marando L, et al (2009) Complement fraction 3 binding on erythrocytes as additional mechanism of disease in paroxysmal nocturnal hemoglobinuria patients treated by eculizumab. Blood; 113(17):4094-100.

Risitano AM (2016) Paroxysmal nocturnal hemoglobinuria in the era of complement inhibition. American Journal of Hematology; Vol. 91, No. 4.

Sridhar S, Greenwood B, Head C, et al (2015) Global incidence of serogroup B invasive meningococcal disease: a systematic review. Lancet Infect Dis; 15(11:)1334-46.

Subías Hidalgo M, Martin Merinero H, López A, et al (2017) Extravascular hemolysis and complement consumption in Paroxysmal Nocturnal Hemoglobinuria patients undergoing eculizumab treatment. Immunobiology; 222(2):363-371.

15 Appendix 1: Liver Event Definitions and Follow-up Requirements

Table 15-1 Liver Event Definitions

Definition	Thresholds
Potential Hy's law cases	• ALT or AST > 3 × ULN and TBL > 2 × ULN without initial increase in ALP to > 2 × ULN
ALT or AST elevation with coagulopathy	• ALT or AST > 3 × ULN and INR > 1.5 (in the absence of anticoagulation)
ALT or AST elevation accompanied by symptoms	• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash, or eosinophilia
Isolated ALT or AST elevation	• ALT or AST > 8 × ULN • 5 x ULN < ALT/AST ≤ 8 x ULN • 3 x ULN < ALT/AST ≤ 5 x ULN
Isolated ALP elevation	• ALP > 2 × ULN (in the absence of known bone pathology)
Others	• Any clinical event of jaundice (or equivalent term) • Any adverse event potentially indicative of liver toxicity

Table 15-2 Actions required for Liver Events

Criteria	Actions required
Potential Hy's Law case ALT or AST elevation with coagulopathy ALT or AST elevation accompanied by symptoms Isolated ALT or AST elevation > 8 × ULN Jaundice	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete CRFs per liver event guidance*
Isolated ALT or AST elevation > 5 to ≤ 8 × ULN	• If confirmed, consider interruption or discontinuation of study drug • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete CRFs per liver event guidance*
Isolated ALT or AST elevation > 3 to ≤ 5 × ULN (patient is asymptomatic)	• Monitor liver chemistry tests two or three times weekly • Repeat liver chemistry tests within 48-72 hours
Isolated ALP elevation	• If elevation is confirmed, measure fractionated ALP; if >50% is of liver origin, establish hepatic causality • Complete CRFs per liver event guidance*
Any AE potentially indicative of liver toxicity	• Consider study treatment interruption or discontinuation • Hospitalize if clinically appropriate • Complete CRFs per liver event guidance*

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

Table 15-3 Exclusion of underlying liver disease

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-HAV; HBSAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

16 Appendix 2: Specific Renal Alert Criteria and Actions

Table 16-1 Specific Renal Alert Criteria and Actions

Criteria	Action required
Serum creatinine (sCr) increase 25 – 49% compared to baseline	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase ≥ 50%	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider hospitalization and specialized treatment
Protein-creatinine or albumin-creatinine ratio increase ≥ 2-fold or new onset dipstick proteinuria ≥ 1+ or Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol; or Protein-creatinine ratio (PCR)≥ 150 mg/g or >15 mg/mmol	• Consider causes and possible interventions • Assess serum albumin & serum protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset glucosuria on urine dipstick (unless related to concomitant treatment, diabetes)	Assess & document: • Blood glucose (fasting) • Serum creatinine • Urine albumin-creatinine ratio
New hematuria on dipstick	Assess & document: • Urine sediment microscopy • Assess sCr and urine albumin-creatinine ratio • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

Additional specialized assessments are available to assess renal function or renal pathology. (Note: In exceptional cases when a nephrologist considers a renal biopsy, it is strongly recommended to make specimen slides available for evaluation by Novartis to potentially identify project-wide patterns of nephrotoxicity.)

Whenever a renal event is identified, a detailed subject history and examination are indicated to identify, document and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5 min rest, with an appropriate cuff size)
- Signs and symptoms such as fever, headache, shortness of breath, back or abdominal pain, dysuria, hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other potential causes of renal dysfunction, e.g., dehydration, hemorrhage, tumor lysis

Table 16-2 Follow-up of renal events

Action	Follow up
Assess*, document and record in the Case Report Form (CRF) or via electronic data load. Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc) in the CRF.	• Urine dipstick and sediment microscopy • Blood pressure and body weight • Serum creatinine, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output • Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline)
Monitor subject regularly (frequency at investigator's discretion) until:	or • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.

*Urine osmolality: in the absence of diuretics or chronic kidney disease this can be a very sensitive metric for integrated kidney function that requires excellent tubular function. A high urinary osmolality in the setting of an increase in sCr will point toward a "pre-renal" cause rather than tubular toxicity.