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LFG316

Clinical Trial Protocol CLFG316X2201 / NCT02534909

An open-label proof of concept study to assess the efficacy, safety and pharmacokinetics of LFG316, an anti-C5 monoclonal antibody in patients with paroxysmal nocturnal hemoglobinuria (PNH)

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct.

Notification of serious adverse events

Refer to Section 9.2 of the protocol for definitions and reporting requirements for Serious Adverse Events (within 24 hours after awareness of the SAE to the local Novartis Chief Medical Office and Patient Safety Department and notify the Clinical Trial Leader).

Contact information is listed in the Site Operations Manual.

Table of contents

Commercially Confidential Information (CCI)

List of tables

List of figures

List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
b.i.d.	twice per day
BMI	Body Mass Index
BUN	blood urea nitrogen
CD-ROM	compact disc – read only memory
CDS	Core Data Sheet (for marketed drugs)
CFR	Code of Federal Regulations
CK	creatinine kinase
CMO&PS	Chief Medical Office and Patient Safety
CRF	Case Report/Record Form (paper or electronic)
CO_2	carbon dioxide
CRO	Contract Research Organization
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
CTRD	Clinical Trial Results Database
CV	coefficient of variation
DDI	Drug-drug interaction
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EORTC	European Organization for Research and Treatment of Cancer

FB	Factor B

FDA	Food and Drug Administration
FIH	First in human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GPI	glycosylphosphatidylinositol
γ-GT	Gamma-glutamyl transferase
h	hour
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IG	Immonogenicity
IgAN	IgA nephropathy
IgG1	Immunoglobulin G 1
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine system
i.v.	intravenous
LC/MS	Liquid Chromatography/Mass Spectrometry
LDH	lactate dehydrogenase
LFT	Liver function test

LLN	lower limit of normal
LPS	Lipopolysaccharides
mAb	Monoclonal antibodies
MAC	membrane attack complex
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
MN	membranous nephropathy
ml	milliliter(s)
NOAEL	no observed adverse effect level

NOVDD	Novartis Data Dictionary
OC/RDC	Oracle Clinical/Remote Data Capture
PA	posteroanterior
PD	pharmacodynamic(s)
PFT	pulmonary function test(s)
PK	pharmacokinetic(s)
PNH	Paroxysmal nocturnal hemoglobinuria
p.o.	oral(ly)

RBC	red blood cell(s)
REB	Research Ethics Board
SAD	single-ascending dose
SAE	serious adverse event
s.c.	subcutaneous
SCC	squamous cell carcinoma
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SD	standard deviation
SOM	site operations manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
ULN	upper limit of normal
ULQ	upper limit of quantification
WBC	white blood cell(s)
WHO	World Health Organization

Pharmacokinetic definitions and symbols

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]
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]
Cmax	The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume]
Tmax	The time to reach the maximum concentration after drug administration [time]

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Protocol synopsis

Protocol number	CLFG316X2201
Title	An open-label proof of concept study to assess the efficacy, safety and pharmacokinetics of LFG316, an anti-C5 monoclonal antibody in patients with paroxysmal nocturnal hemoglobinuria (PNH)
Brief title	Proof of concept study to assess the efficacy, safety and pharmacokinetics of LFG316 in patients with paroxysmal nocturnal hemoglobinuria (PNH)
Sponsor and Clinical Phase	Novartis Pharma Services AG Phase II
Intervention type	Biologic
Study type	Interventional
Purpose and rationale	To determine whether LFG316 administered via i.v. infusion can induce a hematological response, as measured by reduction in hemolytic activity, in patients with PNH. Period 4 was implemented to convert PNH patients receiving i.v. infusion of LFG316 to oral treatment with LNP023 in order to enable participation in the planned LNP023 long-term extension study CLNP023C12001B, and to assure continuous treatment of the study patients who otherwise have limited treatment options.
Primary Objective(s)	To assess the effect of LFG316 on the reduction of intravascular hemolysis in PNH patients as determined by measuring changes in serum LDH levels within 4 weeks of treatment and over the entire treatment period.
Secondary Objectives	To assess the tolerability and pharmacokinetics of LFG316 in patients with PNH. Standard safety monitoring with increased vigilance for infections will be applied, and measurement of serum concentrations of LFG316.
Study design	Open-label, non-controlled study in patients with PNH. The study will consist of a 60-day screening period to assess eligibility and conduct vaccinations if required (for all patients not previously vaccinated at least 2 weeks prior to first dosing or if prior vaccination cannot be confirmed). During the treatment period 1, all patients will receive infusions of LFG316 every 14 days. At the end of period 1, efficacy on hemolytic activity by serum LDH will be assessed. All patients will be allowed to enter the optional treatment period 2 and subsequently period 3, and will undergo all assessments specified by the Protocol Assessment Schedule. The extension period 3 will be followed by a Study Completion evaluation approximately 8 weeks after the last drug administration. Patients participating in extension period 3 (up to 260 weeks) will roll over from the last dosing visit of period 2 to the first visit (which includes drug administration) of period 3. The same dosing interval applied in period 1 and 2 needs to be respected between the last dosing visit of period 2 (Week 52 of treatment) and the first visit of period 3. The LFG316 treatment for all patients will be completed by end of 2021 regardless of each individual treatment period. Patients participating in period 3 will have the option to complete the period 3 Follow up and Study Completion evaluation or to continue with study period 4 which is a pre-requisite for their eligibility to join the long-term extension

	study CLNP023C12001B. During period 4, which will last approximately 21 weeks, treatment will be converted from intravenous LFG316 to oral LNP023. During the first 4 weeks patients will continue to receive LFG316 20 mg/kg every two weeks (total of two administrations) in addition to oral administration of LNP023 200 mg b.i.d. After 4 weeks, patients will discontinue LFG316 and will proceed with LNP023 200 mg b.i.d. for approximately 16 weeks (+/- 28 days).
Population	The study population will be comprised of male and female PNH patients not currently receiving eculizumab therapy and who fulfill all other eligibility criteria.
Key inclusion criteria	• Male and female patients ≥18 years old with a diagnosis of PNH prior to screening. Based on local requirements (applicable in Czech Republic) only patients between the age of 18-65 (inclusive) with a diagnosis of PNH prior to screening may be eligible for inclusion in this study. • A documented PNH clone size of ≥10% by RBCs and/or granulocytes, measured by GPI-deficiency on flow cytometry • Serum LDH levels at least 1.5-fold above the upper limit of normal (ULN) at screening • Negative pregnancy test for women of child bearing potential at screening • Previous vaccination against Neisseria meningitidis types A, C, Y and W-135 is required at least 2 weeks prior to first dosing. Vaccination against meningitidis type B should be conducted if available and acceptable by local regulations, at least 2 weeks prior to first dosing. Subjects to be included in this study after protocol amendment 6 also have to fulfill criterion: • PNH patients that are carriers of the C5 gene minor variants as defined by nucleic acid changes that lead to amino acid exchanges in position p.Arg885 Inclusion Criteria for period 4: • Patients participating in period 3 of the current study who are willing to join long-term extension study with LNP023 (CLNP023C12001B) • Previous vaccination for the prevention of *S. pneumoniae* and *H. influenzae* at least 2 weeks prior to first dosing with LNP023 if locally available. If LNP023 treatment has to start earlier than 2 weeks post vaccination, prophylactic antibiotic treatment must be initiated.

Key exclusion criteria	• Known or suspected hereditary complement deficiency • History of recurrent meningitis, history of meningococcal meningitis despite vaccination • Presence or suspicion (based on judgment of the investigator) of active bacterial infection within 2 weeks prior to first dose of LFG316, or recurrent bacterial infections • Under active therapy with other agents interfering with the complement system • Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 50 days after the last dose of LFG316.
Investigational and reference therapy	Periods 1 to 3: LFG316 will be administered via i.v. infusion every 14 days to all patients participating to the study. Period 4: During the first 4 weeks patients will continue to receive LFG316 20 mg/kg every two weeks (total of two administrations) in addition to oral administration of LNP023 200 mg b.i.d. After 4 weeks, patients will discontinue LFG316 and will proceed with LNP023 200 mg b.i.d. for approximately 16 weeks.
Efficacy/PD assessments	Serum LDH
Safety assessments	Laboratory Evaluations ECG Pregnancy Vital signs / Height and weight
Other assessments	Commercially Confidential Information
Data analysis	The primary efficacy variable is response rate where a patient will be considered a responder if the percentage reduction from baseline in serum LDH is at least 60% at any time up to and including week 4 for that patient. Thorough verification and analysis of the LDH response will be also conducted on the overall treatment duration. Total LFG316 concentrations will be expressed as µg/mL. Commercially Confidential Information All information obtained on adverse events will be displayed as summary and by subject.
Key words	PNH, LFG316, C5, LNP023

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). The deficiency in CD55 & CD59 allows for uncontrolled C3 activation & opsonization of RBCs. Subsequently, assembly of the membrane attack complex (MAC) from Complement factors C5, C6, C7, C8, C9 causes intravascular lysis of RBCs. The resulting paroxysms of hemolysis lead to the release of high amounts of free hemoglobin into the circulation, which is reflected by hemoglobinuria and a drop in circulating haptoglobin. The clinical manifestations of PNH are multifold and include fatigue, abdominal pain and smooth muscle dystonias. The highly elevated risk for thromboembolic events is the most important cause of mortality. Frequent blood transfusions are required to treat anemia in PNH patients experiencing severe episodes of hemolysis.

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LFG316 is an anti-C5 antibody that binds to a different, remote epitope on C5 compared with eculizumab.

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Beside the well-described intravascular hemolysis, PNH patients frequently present with persistent extravascular hemolysis despite blockade of the complement Factor C5 leading to continuous red blood cell hemolysis, reactive reticulocytosis, increased bilirubin and LDH levels (Hill et al 2010; Risitano et al 2009).

LNP023 is a novel oral small molecular weight compound that reversibly inhibits FB of the complement alternative pathway (AP) thereby preventing C3 fragments from opsonizing PNH erythrocytes leading to less extravascular and intravascular hemolysis (Risitano and Marotta 2016; Subias Hidalgo et al 2017). It is thought that blockade of the AP with oral LNP023 has the potential to prevent both intra- and extravascular hemolysis and therefore offer therapeutic superiority to the anti-C5 therapy.

1.1.1 Relevant data summary

The most relevant data for the present study are summarized in the sections below. For detailed information, please refer to the respective Investigators Brochures.

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1.1.1.3 Human safety and tolerability data

1.1.1.3.1 LFG316

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Eculizumab was approved in 2007 for the treatment of PNH and in 2011 for atypical hemolytic uremic syndrome. The most important serious safety finding with eculizumab therapy is the increased risk of Neisseria infections. Therefore, patients are vaccinated against *N. meningitides* prior to receiving eculizumab. In some countries, the prophylactic administration of antibiotics is required. Similar measures will be applied in the present study.

1.1.1.3.2 LNP023

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There are N=29 PNH patients receiving b.i.d dose between 25 and 200 mg LNP023 in CLNP023X2201 and CLNP023X2204 studies. The approximately 3 months core parts of both studies are completed and patients continue to receive LNP023 in an extension phase (total treatment duration between approximately 10 months and 2.5 years depending on the patient).

In addition, there are several ongoing studies in C3 glomerulopathy, IgA nephropathy (IgAN) and membranous nephropathy (MN).

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Known potential safety risks of LNP023 based on the mechanism of action (complement FB inhibition) include susceptibility to infections. Patients with mutations of FB are generally healthy, but have impaired resistance against encapsulated bacterial infections (Slade et al 2013).

There have been no serious infections reported in PNH patients treated with LNP023, the most significant non-serious infections being recurrent herpes virus infections, bilateral otitis and mild acneiform lesions in one patient each.

Of note, a suspected unexpected serious adverse reaction (SUSAR) of pneumococcal pneumonia with septic shock and acute respiratory distress syndrome (ARDS) was recently reported on the C3 glomerulopathy trial in a multiply immunosuppressed patient with a history of renal transplantation. This first report of an infection with encapsulated bacteria was considered by the Investigator as suspected to be related to LNP023, but also to the other immunosuppressive agents the patient was on concomitantly (i.e., prednisone, cyclosporin, mycophenolate mofetil) and triggered the issuance of an Investigator Notification. The patient completely recovered.

1.1.1.4 Human pharmacokinetic data

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1.1.1.5 Human pharmacodynamic data

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1.2 Study purpose

The purpose of the study is to determine whether LFG316 administered via i.v. infusion at 20 mg/kg once every 14 days can induce a hematological response, as measured by reduction in hemolytic activity, in patients with PNH. Commercially Confidential Information

Period 3 (extension of treatment duration) was implemented to ensure a seamless continuation of treatment for LFG316-responsive patients enrolled in the study.

Period 4 is implemented to convert PNH patients receiving i.v. infusion of LFG316 to oral treatment with LNP023, thereby allowing them to be considered for participation in the planned long-term extension study CLNP023C12001B.

2 Study objectives

2.1 Primary objective(s)

Objective	Endpoint
• To assess the effect of LFG316 on the reduction of intravascular hemolysis in PNH patients	• Reduction in serum LDH levels within the first 4 weeks of treatment • Reduction in serum LDH levels over the entire treatment period.

2.2 Secondary objective(s)

Objective	Endpoint
• To assess the tolerability and pharmacokinetics of LFG316 in patients with PNH	• Standard safety monitoring with increased vigilance for infections • Measurement of serum concentrations of LFG316

2.3 Exploratory objective(s)

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3 Investigational plan

3.1 Study design

This is an open-label, non-controlled study in patients with PNH. Approximately 10 patients will be enrolled in the study. At the time that Protocol amendment v07 is effective, no additional patients will be enrolled. The study drug will be administered via i.v. infusion at the dose level of 20 mg/kg every 14 days. Patients participating in study will have an option to either complete period 3 Follow up and Study Completion evaluation or continue in study period 4 that is pre-requisite to join the long-term extension study CLNP023C12001B, that is separate to this study protocol. Patients who are potentially eligible and willing to participate in the LNP023 long-term extension study will join period 4, where treatment will be converted from LFG316 to LNP023 200 mg b.i.d.

The study will consist of a 60-day screening period to assess eligibility and conduct vaccinations if required (for all patients not previously vaccinated at least 2 weeks prior to first dosing or if prior vaccination cannot be confirmed). An extensive screening window (up to 60 days) is planned in order to comply with local vaccination requirements, if available and deemed necessary at the investigator's discretion. Safety evaluation assessments requiring blood and urine samplings, pregnancy test, pulmonary function test, ECG, patient reported outcomes, and assessment of number of blood transfusions should be performed no longer than 4 weeks prior

to the planned dosing day. Subjects who meet the eligibility criteria at screening will be admitted to baseline (Day 1) evaluations. The patients will enter treatment period 1, and will receive infusions of LFG316 every 14 days, days 1, 15 and 29 (3 administrations).

At the end of period 1, efficacy on hemolytic activity by serum LDH will be assessed. All patients will then be allowed to enter the optional treatment period 2, and will receive infusions of LFG316 every 14 days, and undergo the efficacy, PK, CCI and safety assessments for additional 48 weeks.

Following the 48-week treatment period 2, LFG316-responsive patients (assessed based on investigator's judgment) will be allowed to enter an additional third extension period of up to 260 weeks (extension period 3).

The LFG316 treatment for all patients will be completed by end of 2021 regardless of each individual treatment period.

Patients participating in extension period 3 will roll over from the last dosing visit of period 2 to the first visit (which includes drug administration) of period 3. The same dosing interval applied in Period 1 and 2 will be applied between the last dosing visit of Period 2 and the first visit of Period 3.

Period 4 can be initiated as directed by Sponsor and will last approximately 21 weeks. During the first 4 weeks patients will continue to receive LFG316 20 mg/kg every two weeks (total of two administrations) in addition to oral administration of LNP023 200 mg b.i.d. After 4 weeks, patients will discontinue LFG316 and will proceed with LNP023 200 mg b.i.d. monotherapy for approximately 16 weeks (+/- 28 days). Patients who participate in period 4 can join the long-term extension study CLNP023C12001B as soon as their eligibility is confirmed and study CLNP023C12001B is open to receive patients. There should be no LNP023 treatment gap between the studies. Please refer to Section 7.1 for guidance regarding safety monitoring and LNP023 down-titration in case of LNP023 treatment discontinuation.

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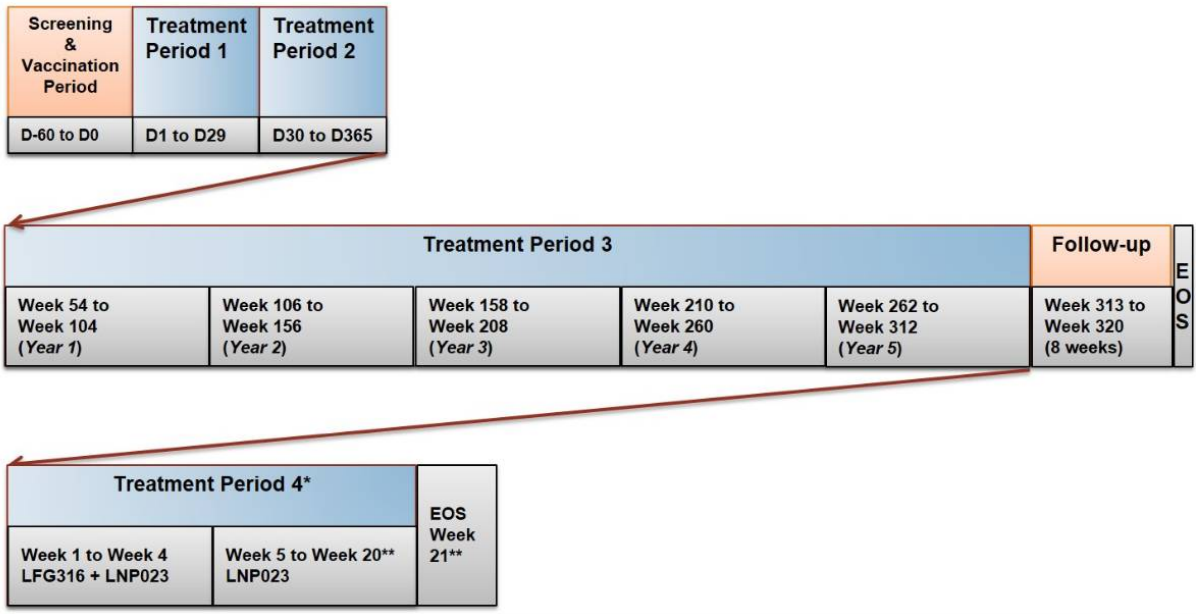
For patients not participating in the period 4, the extension period 3 will be followed by a Study Completion evaluation approximately 8 weeks after the last drug administration. Patients who discontinue treatment prematurely during any of the study periods will be followed for 8 weeks after discontinuation, and will similarly undergo a study completion visit. The 8 weeks follow-up period will start the day after the last drug administration (both for patients completing treatment and patients prematurely discontinuing), and will comprise one visit after approximately 4 weeks, and a study completion visit after approximately 8 weeks from the last drug administration. Safety assessments will include physical examinations, ECG, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, urinalysis) and adverse event monitoring.

Patients participating in period 4, will complete their Study Completion evaluation approximately one week after last LNP023 treatment administered as a part of this study.

Figure 3-1 Study design



*Period 4 is applicable only for the patients who are potentially eligible and wish to participate in the long-term extension study CLNP023C12001B

**+/-28 days

3.2 Rationale of study design

The design of this study addresses the primary objective of reduction of hemolysis in patients with PNH and takes into account the rarity of this disease and the objective nature of the measurement, i.e. reduction in serum LDH levels.

This non-controlled study was designed as a non-placebo-controlled study since the absence of a placebo response in this patient population can be assumed, based on published data and the nature of the primary outcome measure, which is a biochemical parameter. This study will be limited to patients who require treatment but are currently not treated with eculizumab.

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3.3 Rationale of dose/regimen, duration of treatment

3.3.1 LFG316

LFG316 will be administered at 20 mg/kg as i.v. infusion every 14 days throughout all periods. Duration of the infusion will vary between 40 minutes and 2 hours as described in provided separately pharmacy manual. Commercially Confidential Information

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The dosing regimen may be adjusted in period 2 to achieve sufficient drug exposure to warrant safety of the patient, e.g. in case of breakthrough hemolysis towards the end of a dosing interval. In period 1 dosing should not be changed, unless judged unavoidable to warrant patient's safety by the investigator. Details are outlined in Section 6.3.

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Considering the favorable safety profile and exposure levels detected at the 20 mg/kg dose, a dosing regimen of 20 mg/kg every 14 days (2 weeks) was chosen in the present study. The dosing regimen may be adjusted if insufficient duration of benefit is observed, e.g. in case of breakthrough hemolysis towards the end of a dosing interval, as measured by LDH levels.

To date patients up to 82 years old were safely treated with LFG316 and considering lack of any treatment options it is deemed justified to allow the treatment of older PNH patients.

3.3.2 LNP023

The dose of 200 mg LNP023 b.i.d. as continuous treatment has been selected for period 4 of this study based on the available efficacy and safety data obtained at the time of interim analyses from the two ongoing Phase 2 PNH studies and is supported by PKPD modeling results.

In the CLNP023X2201 study in patients with active hemolysis despite treatment with eculizumab, LNP023 at a dose of 200 mg b.i.d. was administered to N=10 PNH patients (Cohort 1) and at a dose of 50 mg b.i.d. to N=6 PNH patients (Cohort 2).

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In the CLNP023X2204 study, enrolling anti-C5 antibody treatment naive patients, participants received LNP023 monotherapy with sequential dose increments at Week 4 from LNP023 25 mg b.i.d. to 100 mg b.i.d (Sequence 1) or LNP023 50 mg b.i.d. to 200 mg b.i.d. (Sequence 2).

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The dose of 200 mg b.i.d. is expected to provide optimal efficacy required for PNH as monotherapy with an adequate safety profile

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In summary, LNP023 at a dose of 200 mg b.i.d. was not only safe and well tolerated by patients in both studies in PNH but demonstrated convincing efficacy as monotherapy measured as efficacious control of both, intra- as well as extravascular hemolysis. The same LNP023 dose of 200 mg BID was tested safe, well tolerated and efficacious in patients with IgA nephropathy (study CLNP023X2203; NCT04557462) and C3 glomerulopathy (CLNP023X2202; NCT03832114), further supporting its use in this study. The taper down of 2 weeks was included to mitigate potential risk of increased hemolysis after LNP023 discontinuation. This will be only implemented for patients who cannot complete period 4 or continue LNP023 treatment in long-term extension study.

Four weeks of LFG316 and LNP023 co-exposure in period 4 allows to establish LNP023 steady state concentration and efficacious complement Factor B inhibition before discontinuing the complement Factor C5 neutralization with LFG316. Based on data from study CLNP023X2201 (see above), co-exposure of LNP023 and anti-C5 therapy is considered safe and well tolerated.

A treatment duration with LNP023 is thought to fulfill the required minimum of 3 months stable conditions under LNP023 monotherapy that allows patients to join the long-term extension study CLNP023C12001B.

3.4 Rationale for choice of comparator

Not applicable.

3.5 Purpose and timing of interim analyses/design adaptations

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3.6 Risks and benefits

PNH is a hematological disease with various severe morbidities and increased mortality, mostly due to thromboembolic complications. The only approved and effective therapy is the anti-C5 antibody eculizumab. Commercially Confidential Information

CCI . Classical treatment regimens are based on blood transfusion, anticoagulation, and support of erythropoiesis. They are poorly efficacious and associated with a high burden to the patients.

LFG316 has comparable PK/CCI properties as eculizumab and is therefore expected to effectively inhibit hemolysis and show similar clinical benefit in all PNH patients including carriers of the variant described above.

The main risks of anti-C5 therapies are related to infections. To date, no infection has been observed in the limited number of subjects who have received intravenous LFG316. The most important adverse effect associated with systemic eculizumab, however, is infection by Neisseria (N). meningitidis (e.g. meningitis). These infections are consistent with reports of occasional but recurrent meningococcal infections seen in patients with total hereditary C5 deficiency (Rosenfeld et al 2006; Haeney et al 1980; Cesbron et al 1985; Sanal et al 1992; Delgado-Cerviño et al 2005; López-Lera et al 2009; Zerzri et al 2010); pneumococcal infections were also reported in hereditary complement deficiency. Where measured, affected (homozygous) patients showed no measurable circulating C5 protein or complement-mediated hemolytic activity. Importantly, heterozygous C5-deficient relatives have roughly half the normal levels of circulating C5 and hemolytic activity but do not appear to be at risk for infections, thus suggesting that the risk increases only in cases of >50% inhibition of C5.

The risk to patients in this trial will be minimized by adherence to the eligibility criteria, counseling, close clinical monitoring, and meningococcal vaccination prior to administration of LFG316, due to the risk of infection with encapsulated bacteria.

For patients under treatment with any other immunosuppressive drugs during the study, treatment with prophylactic antibiotics is strongly recommended. Overall, the potential benefits of anti-C5 therapy outweigh the risks in this population of PNH patients.

The study is divided into 4 parts: treatment period 1 (29 days), during which a total of approximately 350 mL of blood will be collected, treatment period 2 (335 days), during which approximately 700 mL blood will be collected, treatment period 3 (up to 5 years duration), during which the maximum collected blood volume will be approximately 1300 mL, and period 4 (approximately 5 months) when approximately 220 mL of blood will be collected. The maximum blood volume over any 12 week period will not exceed 450 ml. Additional samples for monitoring of any safety findings would be in addition to this. This is not considered to be a risk for this population.

Women of child bearing potential should be informed that taking the study drug 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 for the duration of the study. If there is any question that the subject will not reliably comply, they should not be entered in the study.

There may be unknown risks of LFG316 which may be serious and unforeseen.

In the absence of any additional anticipated or known risks of complement inhibition in relationship with COVID-19, the benefit/risk ratio of this study protocol and of both investigational drugs in particular, LFG316 and LNP023, remains unchanged during the COVID-19 pandemic.

3.6.1 Risks and benefits for period 4

The risks associated with the use of LNP023 are those inferred by its mechanism of action as well as the findings of preclinical safety studies. The most relevant risks and mitigation strategies are described below and a more comprehensive description of safety findings to date is available in Section 1.1.1.3.2 and in the IB.

Based on its mechanism of action, the main potential risk of LNP023 is infection-related. An intact complement system is particularly important for the defense against encapsulated bacteria (e.g., *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Hemophilus influenzae*). Patients with factor B loss-of-function mutations are more susceptible to such infections (Slade et al 2013). The mitigation strategy is to vaccinate patients before the first LNP023 treatment. If LNP023 treatment has to start earlier than 2 weeks post vaccination, prophylactic antibiotic treatment must be initiated. Data suggest that the protective effect of vaccination is maintained after blockade of the AP, but not after C5 blockade (Konar and Granoff 2017). In addition, patients will be instructed to contact the Investigator immediately in case of any signs or symptoms of infection (listed on a "Patient Card" for participant awareness), and relevant AEs will be reviewed on a regular basis.

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Regarding the potential safety risks mentioned above, to date, there have been no serious infections reported in PNH patients, although a SUSAR of pneumococcal pneumonia and sepsis was recently reported on the C3 glomerulopathy trial in a severely immunosuppressed patient with a history of renal transplantation (see Section 1.1.1.3.2). Considering implementation of the vaccinations and close monitoring, the risk for serious infection during LNP023 treatment is still considered to be low. Finally, there have been no serious adverse events related to the other potential risks in any of the clinical studies.

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The risk to subjects in this trial receiving LNP023 will be minimized by adherence to the eligibility criteria, close clinical monitoring, pre-defined stopping rules, periodic review of the safety data, and guidance for the investigators in the Investigator's Brochure.

To note, 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 Exclusion Criteria. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

4 Population

The study population will be comprised of male and female PNH patients not currently receiving eculizumab therapy and who fulfill all other eligibility criteria. Previous response or failure to respond adequately to eculizumab should be documented in all patients who are carriers of the Commercially Confidential Information

Patients must be ≥ 18 years old diagnosed with PNH prior to screening; both males and females will be allowed to enter the study and background therapy with eculizumab is not permitted (wash-out time required: 8 weeks).

Approximately 10 patients will be enrolled.

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

Subject selection is to be established by checking through all eligibility criteria at screening. 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.

4.1 Inclusion criteria

Subjects eligible for inclusion in this study have to fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed
2. Male and female patients ≥18 years old with a diagnosis of PNH prior to screening. Based on local requirements (applicable in Czech Republic) only patients between the age of 18-65 (inclusive) with a diagnosis of PNH prior to screening may be eligible for inclusion in this study.
3. A documented PNH clone size of ≥10% by RBCs and/or granulocytes, measured by GPI-deficiency on flow cytometry
4. Serum LDH levels at least 1.5-fold above the upper limit of normal (ULN) at screening
5. Patients receiving treatment with corticosteroids and/or other immunosuppressive regimens may continue treatment throughout the study, if indicated for treatment of autoimmune disease (e.g. aplastic anemia). It is strongly recommended, but is at the investigator's discretion, that patients receive appropriate prophylactic antibiotics (e.g. ciprofloxacin, penicillin, erythromycin) while on treatment with any type of concomitant immunosuppressive agent other than LFG316 (including corticosteroids).
6. Negative pregnancy test for women of child bearing potential at screening
7. Previous vaccination against Neisseria meningitidis types A, C, Y and W-135 is required at least 2 weeks prior to first dosing. Vaccination against meningitidis type B should be conducted if available and acceptable by local regulations, at least 2 weeks prior to first dosing. Further information available in Section 8.3.7.
8. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

Subjects to be included in this study after protocol amendment 6 also have to fulfill criterion:

9. PNH patients that are carriers of the C5 gene minor variants as defined by nucleic acid changes that lead to amino acid exchanges in position p.Arg885

Additional inclusion criteria for period 4

10. Patients participating in period 3 of the current study who are willing to join long term extension study with LNP023 (CLNP023C12001B)
11. Previous vaccination for the prevention of *S. pneumoniae* and *H. influenzae* at least 2 weeks prior to first dosing with LNP023 if locally available. If LNP023 treatment has to start earlier than 2 weeks post vaccination, prophylactic antibiotic treatment must be initiated.

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this 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.

1. Known or suspected hereditary complement deficiency.
2. History of hematopoietic stem cell transplantation.
3. Participation in any other investigational drug trial or exposure to other investigational agent, device, or procedure within 30 days or 5-times the half-life prior to screening. Note: clinical trials solely involving over-the-counter vitamins, off label use of drugs within published standard of care guidelines, supplements, or diet do not exclude an otherwise eligible patient.
4. Female patients who are pregnant or breastfeeding, or intended to conceive during the course of the study.
5. History of recurrent meningitis, history of meningococcal meningitis despite vaccination.
6. Presence or suspicion (based on judgment of the investigator) of severe active bacterial infection within 2 weeks prior to first dose of LFG316, or severe recurrent bacterial infections.
7. A positive HIV test result.
8. Under active therapy with other agents interfering with the complement system (e.g. eculizumab) Wash-out time should be at least 5 half-lives, approximately 8 weeks for eculizumab.
9. 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.
10. Either one of the following laboratory abnormalities at screening:
    a. Neutrophils $<0.5 \times 10^9$/L
    b. Platelets $<30 \times 10^9$/L
11. Co-morbidities that are a likely caused by underlying autoimmune diseases other than PNH, e.g. kidney disease in the context of lupus nephritis, ANCA-associated vasculitis.
12. 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.
13. History of hypersensitivity to a drug of the same class (human IgG1 mAb) or any other excipient of the formulation.

14. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 50 days after the last dose of LFG316. Highly effective contraception methods include:
    c. Total abstinence (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
    d. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    e. 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
    f. Combination of any two of the following (i+ii or i+iii, or ii+iii):
        i. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
        ii. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
        iii. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository. For UK: with spermicidal foam/gel/film/cream/vaginal suppository
    g. In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
    h. 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) or tubal ligation at least six weeks prior to screening. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential. This group does not need to use contraception.

Note: In the case where a safety laboratory assessment at screening is outside of the range, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the subject is excluded from the study, unless the abnormal value is attributed to the underlying disease (PNH) by the investigator. Re-screening of patients may be permitted but has to be discussed with the Novartis clinical team.

15. Prohibited medication as specified in Section 5.2

5 Restrictions for Study Subjects

During recruitment, screening/informed consent review, and baseline visit, the subjects must be informed and reminded of the following restrictions:

5.1 Contraception requirements

Please refer to exclusion criteria (Section 4) for details of contraception requirements for the study.

5.2 Prohibited treatment

Use of the treatments displayed in the table below is NOT allowed after start of the study drug:

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5.3 Dietary restrictions

No restrictions.

5.4 General restrictions

No restrictions.

6 Treatment

6.1 Study treatment

Details on the storage and management of study medication and instructions for prescribing and taking study treatment are outlined in Section 3 of the Site Operations Manual and in the Pharmacy Manual.

For the first dosing with LFG316, weight collected at baseline visit should be used for dose calculation. For any subsequent dosing, most recently collected pre-dose weight should be used for dose calculation.

6.1.1 Investigational treatment

The investigational drug, LFG316 100 mg Lyophilisate in Vials or 500 mg Liquid in Vials will be provided by Novartis, and supplied to the Investigator.

LNP023 10 and 50 mg hard gelatin capsules will be provided in the open label patient specific kits.

6.1.2 Additional study treatment

Permitted concomitant medications are listed below:

- Erythropoietin
- Corticosteroids and/or other immunosuppressive regimens may be continued throughout if warranted for treatment of autoimmune disease (e.g. aplastic anemia). It is strongly recommended, but is at the investigator's discretion, that patients receive appropriate prophylactic antibiotics (e.g. ciprofloxacin, penicillin, erythromycin) while on treatment with any type of concomitant immunosuppressive agent other than LFG316 (including corticosteroids)
- Anticoagulants, e.g. coumarins, low molecular-weight heparins, factor Xa inhibitors, Thrombin inhibitors
- Iron supplements & folic acid
- Iron depletion therapy as required
- Blood transfusions as required
- Analgesic agents
- Antibiotics, antivirals

Any dose adjustments or new concomitant treatments must be recorded in the relevant eCRF page.

6.2 Treatment arms

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6.3 Permitted dose adjustments of study treatment

Study drug dose adjustments should generally be avoided, particularly in period 1.

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There is no dose adjustment allowed for LNP023 treatment in period 4 except for down-titration in case of LNP023 discontinuation. Down-titration is also recommended for patients who start LNP023 treatment in period 4 and do not join long-term extension study (Section 7.1).

6.4 Treatment assignment

Patient numbers will be assigned in ascending, sequential order to eligible subjects (see Site Operations Manual for details). The investigator will enter the treatment number on the CRF.

6.5 Treatment blinding

Not applicable. This study uses an open-label single treatment design.

6.6 Emergency breaking of assigned treatment code

Not applicable.

6.7 Treatment exposure and compliance

LFG316 will be administered at the dose level of 20 mg/kg via intravenous infusion by the Investigator or designated study staff over approximately 2 hours in Period 1 and between 40 minutes and 2 hours in Periods 2 and 3 (please refer to Pharmacy Manual), and therefore compliance with the planned treatment will be assumed since infusions will be carried out under close medical supervision at the study sites. Although infusion reactions have not been observed with LFG316 to date, close medical supervision at the study site is requested during the infusion time of LFG316 and up to 2 hours after the end of the infusion during Treatment Period 1. In case of a suspected infusion reaction (e.g. mild rash, general discomfort) the infusion rate should be reduced and vital signs should be monitored continuously. Infusion should be stopped in case of severe reactions with need for intervention, as judged by the investigator (e.g. treatment with glucocorticoids, histamine antagonists, epinephrine, bronchodilators). Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects treated with LFG316, as detailed in Section 8.5.

Applicable for period 4: LNP023 will be administered orally at the patients' home or at the study center (mandatory at days when PK samples are collected). During days 1-28 patients will be receiving both LFG316 every 2 weeks and LNP023 every day. On days 29-141 (+/-28 days), LNP023 will be administered as monotherapy. LNP023 dose diary will be implemented to capture information on missing doses. During the COVID-19 pandemic that limits or prevents on-site study visits, delivery of LNP023 directly to a patient's home is generally permitted in the event the Investigator has decided that an on-site visit by the patient is no longer appropriate or possible, and that it is in the interest of the patient's health to administer the study

treatment even without performing an on-site visit. Implementation will need to be discussed with Novartis. The dispatch of IMP from the site to the patient's home remains under the accountability of the Investigator. In this case, regular phone calls or virtual contacts (at the frequency matching planned study visit) will occur between the site and the patient for instructional purposes, safety monitoring, and discussion of the patient´s health status until the patients can again visit the site.

6.8 Recommended treatment of adverse events

Treatment of AEs should follow standard practice. Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.9 Rescue medication

Use of rescue medication must be recorded on the Concomitant medications/Significant non-drug therapies CRF after start of study drug. Additional doses of LFG316 may be administered in case of hemolytic crisis between infusions (as evidenced e.g. by sudden increase in LDH levels, decrease in Hb and based on Investigator's judgment, and can be discussed with Novartis).

Use of eculizumab or other biologics as a rescue medication would lead to treatment discontinuation, and subjects entering the 8 week safety follow-up. Blood transfusions and other therapeutic measures are permitted, as outlined in Section 6.1.2.

6.10 Concomitant treatment

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 section of the 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.

7 Discontinuation and study completion

7.1 Discontinuation of study treatment

Subjects may voluntarily discontinue study treatment for any reason at any time.

The investigator must discontinue study treatment for a given subject if, on balance, he/she believes that continuation would be detrimental to the subject's well-being.

Study treatment must be discontinued under the following circumstances:

- Subject withdraws consent
- Pregnancy
- Emergence of the following adverse events:
  - Evidence for invasive Neisseria infection
  - In case of other severe systemic or life-threatening infections, treatment discontinuation should be decided on a case-by-case basis

- Use of prohibited treatment as per Section 5.2.
- Any other protocol deviation that results in a significant risk to the subject's safety

Subjects 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). Where possible, they should return for the 8 week safety follow-up, which includes monitoring of intravascular hemolysis after drug discontinuation. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact them as specified in Section 7.2.1.

If treatment with LNP023 has to be discontinued prematurely and immediately (i.e., because of a significant safety risk which warrants immediately stopping LNP023 treatment), it is recommended to promptly re-initiate treatment with Standard of Care (SoC), as judged by the investigator.

Close monitoring of patients for signs and symptoms of hemolysis should be performed upon LNP023 discontinuation. It is recommended to monitor at minimum for: increase in LDH, decrease in hemoglobin level and PNH clone size, increase in serum creatinine, thrombosis, and change in neurological/mental status. If serious hemolysis occurs, the Investigator should consider the following supportive treatments (and recording them in the appropriate CRF pages):

- Blood transfusion (packed RBCs), or
- Exchange transfusion if the PNH RBCs are >50% of the total RBCs by flow cytometry,
- Corticosteroids,
- Anticoagulation,
- Any other supportive treatment or therapy as judged by the investigator.

An End of Study (EoS) visit one week after permanent discontinuation of LNP023 should occur for the assessments as specified in the Assessment schedule.

If treatment with LNP023 has to be discontinued prematurely but it is not warranted to immediately discontinue LNP023 treatment (i.e., discontinuation due to patient/guardian decision or confirmed pregnancy), it is recommended to promptly initiate the available SoC in the country as judged by the investigator. In addition, it should be considered to taper down LNP023 over a period of 14 days:

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Down-titration is also recommended for patients who start LNP023 treatment in period 4 and do not join long-term extension study.

The investigator should consider the proposed monitoring and supportive treatments listed above in case serious hemolysis occurs. During LNP023 tapering, weekly visits are recommended Commercially Confidential Information

The following assessments are recommended: blood hematology and chemistry for parameters specified in Section 8.3.4.

All data collected will be entered in the appropriate CRF page as an unscheduled visit/assessment.

7.2 Study completion and post-study treatment

Each subject will be asked to complete this study in its entirety (period 1, 2 and 3) and they may be offered to enter an additional extension trial, provided LFG316 shows benefit as defined by the response criteria. Patients willing and eligible to join the extension study CLNP023C12001B must participate in period 4.

Study completion is defined as when the last subject completes their End of Study 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.

At a minimum, patients ending participation after period 3, will be contacted for safety evaluations during the 8 week safety follow-up period in which intravascular hemolysis will be monitored, and a final Study Completion Visit will be conducted at the conclusion of the safety follow-up period. A safety follow-up call should be conducted approximately 30 days after last LNP023 administration to confirm he patient has not experienced any SAEs during this post-study period for any patient participating in period 4, who does not roll over into CLNP023C12001B. Documentation of attempts to contact the subject should be recorded in the source documentation The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

7.2.1 Lost to follow-up

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

7.3 Withdrawal of consent

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

Withdrawal of consent occurs only when a subject does not want to participate in the study anymore **and** does not allow further collection of personal data.

If a subject withdraws consent, the investigator must make every effort to determine the primary reason for this decision 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.

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

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

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

7.4 Study stopping rules

Enrollment will be put on hold pending full safety review if more than one unexpected and possibly related SAEs is reported. The study will be stopped if the benefit-risk ratio changes to be unacceptable in this indication.

7.5 Early study termination

The study can be terminated at any time by Novartis.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to subjects enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider subject welfare and safety. Should this be necessary, subjects should be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor will be responsible for informing IRBs/IECs of the early termination of the trial depending on local regulation.

8 Procedures and assessments

Subjects should be seen for all visits on the designated day, with the assessments performed as per schedule, within the allowed "visit/assessment window" specified in the Site Operations Manual.

If the COVID-19 pandemic limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented. Phone calls, virtual contacts (e.g. teleconsultation) or visits by site staff/home nursing service to the patient´s home depending on local regulations and capabilities, can replace on-site study visits, for the duration of the pandemic until it is safe for the patient to visit the site again. Local laboratory to monitor safety might be implemented if feasible.

Table 8-1 Assessment schedule

Study epoch	Screening	Treatment																														
Study phase	Screening	Treatment Period 1					Treatment Period 2 (Extension Period 2)																										
Visit Numbers (internal use only)	1	101	102	103	104	105	201	202	203	204	205	206	207	208	209	210	211	212	213	214	215	216	217	218	219	220	221	222	223	224		
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24	V25	V26	V27	V28	V29	V30		
Day	D -60* to 0	D1	D8	D15	D22	D29	D43	D57	D71	D85	D99	D113	D127	D141	D155	D169	D183	D197	D211	D225	D239	D253	D267	D281	D295	D309	D323	D337	D351	D365		
Inclusion /Exclusion criteria	X																															
Relevant med. History/Current conditions	X																															
Demography	X																															
Physical examination	X	X	X	X	X	X		X				X				X				X				X				X		X		
HIV screen	X																															
Urine drug screen & alcohol test	X	X																														
Vaccination (for all patients not previously vaccinated at least two weeks prior to first dosing or if prior vaccination cannot be confirmed)	X																															
Pregnancy test	X[a]	X				X		X		X		X		X		X		X		X		X		X		X		X		X		
Drug administration		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse Events	As required																															
Concomitant meds/Therapies	X	As required																														
Comments	As required																															
Vital signs and body measurements																																
Body height	X																															
Body weight	X		X			X		X		X		X		X		X		X		X		X		X		X		X		X		
Body temperature	X	X	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X		
Blood pressure / Pulse rate	X	X	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X		
ECG evaluation	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		
Safety Laboratory Evaluations: Hematology (including Reticulocyte counts), Blood chemistry (including serum LDH, free Hbg and haptoglobin)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Number of blood transfusions	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
PNH type III RBCs by flow cytometry	X					X		X		X		X		X		X		X		X		X		X		X		X		X		
Pulmonary Function Test		X				X		X		X		X		X		X		X		X		X		X		X		X		X		
PK blood collection		X[b]		X		X[b]		X[c]		X[c]		X[c]		X[c]		X[c]		X[c]		X[c]		X[c]		X[c]		X[c]		X[c]		X[c]		

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a: Serum pregnancy test required at screening, urine pregnancy test at further time points. Only for post-menopausal women, the hormone measurement (FSH) to confirm post menopausal status required at screening
b: Samples collected pre-and post dose - Post-dose PK samples must be collected only upon infusion completion, and within 2 hours of the end of the infusion
c: Samples collected pre- dose
d: sample to be collected at baseline or at any visit post baseline
* Screening period to enable the conduct of vaccination requirements (if local guidelines requires it, and if deemed necessary at investigator's discretion)

Study epoch	Treatment (continued)																									
Study phase	Treatment Period 3 (Extension Period 3)																									
Visit Numbers (internal use only)	301	302	303	304	305	306	307	308	309	310	311	312	313	314	315	316	317	318	319	320	321	322	323	324	325	326
1st Year Extension	V41	V42	V43	V44	V45	V46	V47	V48	V49	V50	V51	V52	V53	V54	V55	V56	V57	V58	V59	V60	V61	V62	V63	V64	V65	V66
Week	54	56	58	60	62	64	66	68	70	72	74	76	78	80	82	84	86	88	90	92	94	96	98	100	102	104
Day	**379**	**393**	**407**	**421**	**435**	**449**	**463**	**477**	**491**	**505**	**519**	**533**	**547**	**561**	**575**	**589**	**603**	**617**	**631**	**645**	**659**	**673**	**687**	**701**	**715**	**729**
Visit Numbers (internal use only)	401	402	403	404	405	406	407	408	409	410	411	412	413	414	415	416	417	418	419	420	421	422	423	424	425	426
2nd Year Extension	V67	V68	V69	V70	V71	V72	V73	V74	V75	V76	V77	V78	V79	V80	V81	V82	V83	V84	V85	V86	V87	V88	V89	V90	V91	V92
Week	106	108	110	112	114	116	118	120	122	124	126	128	130	132	134	136	138	140	142	144	146	148	150	152	154	156
Day	**743**	**757**	**771**	**785**	**799**	**813**	**827**	**841**	**855**	**869**	**883**	**897**	**911**	**925**	**939**	**953**	**967**	**981**	**995**	**1009**	**1023**	**1037**	**1051**	**1065**	**1079**	**1093**
Visit Numbers (internal use only)	501	502	503	504	505	506	507	508	509	510	511	512	513	514	515	516	517	518	519	520	521	522	523	524	525	526
3rd Year Extension	V93	V94	V95	V96	V97	V98	V99	V100	V101	V102	V103	V104	V105	V106	V107	V108	V109	V110	V111	V112	V113	V114	V115	V116	V117	V118
Week	158	160	162	164	166	168	170	172	174	176	178	180	182	184	186	188	190	192	194	196	198	200	202	204	206	208
Day	**1107**	**1121**	**1135**	**1149**	**1163**	**1177**	**1191**	**1205**	**1219**	**1233**	**1247**	**1261**	**1275**	**1289**	**1303**	**1317**	**1331**	**1345**	**1359**	**1373**	**1387**	**1401**	**1415**	**1429**	**1443**	**1457**
Inclusion /Exclusion criteria																										
Relevant med. History/Current conditions																										
Demography																										
Physical examination	X		X		X		X		X		X		X		X		X		X		X		X		X	
HIV screen																										

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Urine drug screen & alcohol test	X																									
Pregnancy test **(a)**	X		X		X		X		X		X		X		X		X		X		X		X		X	
Drug administration	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Adverse Events	As required																									
Concomitant meds/Therapies	As required																									
Comments	As required																									
Vital signs and body measurements																										
Body height																										
Body weight	X		X		X		X		X		X		X		X		X		X		X		X		X	
Body temperature	X	X	X		X		X		X		X		X		X		X		X		X		X		X	
Blood pressure / Pulse rate	X	X	X		X		X		X		X		X		X		X		X		X		X		X	
ECG evaluation	X			X			X			X			X			X			X			X			X	
Safety Laboratory Evaluations: Hematology (including Reticulocyte counts), Blood chemistry (free Hbg and haptoglobin) (b)	X		X		X		X		X		X		X		X		X		X		X		X		X	
Serum LDH (pre-dose) (b)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis **(b)**	X		X		X		X		X		X		X		X		X		X		X		X		X	
Number of blood transfusions	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PNH type III RBCs by flow cytometry **(b)**	X		X				X				X				X				X				X			
Pulmonary Function Test																										

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PK blood collection **(b)**	X[c]													X[c]												

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a: Serum pregnancy test required at screening of Period 1, urine pregnancy test at further time points. Only for post-menopausal women, the hormone measurement (FSH) to confirm post menopausal status required at screening of Period 1

b: Ad-hoc sampling at unscheduled visits allowed (e.g. safey reasons, loss of efficacy, etc)

c: Samples collected pre- dose

d: If not previously collected in Part 1 and 2 of the study - Samples collected pre- dose, sample collected only one time.

Study epoch	Treatment (continued)																											
Study phase	Treatment Period 3 (Extension Period 3)																										Follow-up	Study Completion
Visit Numbers (internal use only)	531	532	533	534	535	536	537	538	539	540	541	542	543	544	545	546	547	548	549	550	551	552	553	554	555	556	**Visit 173 - Week 316, Day 2213 or 4 weeks from last visit performed** (Internal visit 583)	**Visit 777 - Week 320, Day 2241 or 8 weeks from last visit performed (4 weeks after follow-up)** (Internal visit 599)
4th Year Extension	V121	V122	V123	V124	V125	V126	V127	V128	V129	V130	V131	V132	V133	V134	V135	V136	V137	V138	V139	V140	V141	V142	V143	V144	V145	V146		
Week	210	212	214	216	218	220	222	224	226	228	230	232	234	236	238	240	242	244	246	248	250	252	254	256	258	260		
Day	**1471**	**1485**	**1499**	**1513**	**1527**	**1541**	**1555**	**1569**	**1583**	**1597**	**1611**	**1625**	**1639**	**1653**	**1667**	**1681**	**1695**	**1709**	**1723**	**1737**	**1751**	**1765**	**1779**	**1793**	**1807**	**1821**		
Visit Numbers (internal use only)	557	558	559	560	561	562	563	564	565	566	567	568	569	570	571	572	573	574	575	576	577	578	579	580	581	582		
5th Year Extension	V147	V148	V149	V150	V151	V152	V153	V154	V155	V156	V157	V158	V159	V160	V161	V162	V163	V164	V165	V166	V167	V168	V169	V170	V171	V172		
Week	262	264	266	268	270	272	274	276	278	280	282	284	286	288	290	292	294	296	298	300	302	304	306	308	310	312		
Day	**1835**	**1849**	**1863**	**1877**	**1891**	**1905**	**1919**	**1933**	**1947**	**1961**	**1975**	**1989**	**2003**	**2017**	**2031**	**2045**	**2059**	**2073**	**2087**	**2101**	**2115**	**2129**	**2143**	**2157**	**2171**	**2185**		
Physical examination	X				X				X				X				X				X				X		X	X
Urine drug screen & alcohol test																												X
Pregnancy test **(a)**	X				X				X				X				X				X				X		X	X
Drug administration	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		
Adverse Events	As required																											X
Concomitant meds/Therapies	As required																											X
Comments	As required																											X
Vital signs and body measurements																												
Body height																												
Body weight	X				X				X				X				X				X				X		X	X
Body temperature	X				X				X				X				X				X				X		X	X
Blood pressure / Pulse rate	X				X				X				X				X				X				X		X	X
ECG evaluation	X																				X							X
Safety Laboratory Evaluations: Hematology (including Reticulocyte counts), Blood chemistry (free Hbg and haptoglobin), LDH level (b)	X				X				X				X				X				X				X		X	X
Urinalysis **(b)**	X				X				X				X				X				X				X		X	X
Number of blood transfusions	X																											
PNH type III RBCs by flow cytometry **(b)**									X												X							X

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PK blood collection **(b)**																												X
a: Serum pregnancy test required at screening of Period 1, urine pregnancy test at further time points. Only for post-menopausal women, the hormone measurement (FSH) to confirm post menopausal status required at screening of Period 1																												
b: Ad-hoc sampling at unscheduled visits allowed (e.g. safey reasons, loss of efficacy, etc)																												

Assessment schedule for patients participating in Period 4

Study epoch	Treatment								
Study phase	Treatment Period 4 (Extension Period 4)								Study Completion[4]
Visit Numbers (internal use only)	601	602	603	604	605	606	607	608	**Visit 777**
Period 4 visit number	V1001	V1002	V1003	V1004	V1005	V1006	V1007	V1008	**Day 148**
Day	**1**	**15**	**29**	**36**	**43**	**57**	**85**	**141**	(1 week after last LNP023 dose)
Visit window	**-**	**-**	**±1**	**±1**	**±1**	**±2**	**±2**	**±28**	**±28**
Inclusion/exclusion for period 4*	S[1]								
Physical examination	S[1]	S	S	S	S	S	S	S	S
Pregnancy test	X[1]		X			X	X		X
LFG316 administration	X	X							
LNP023 administration[5]	X[3]								
Body weight	X[1]								X
Body temperature	X[1]	X	X	X	X	X	X	X	X
Blood pressure / Pulse rate	X[1]								X
ECG evaluation	X[1]								X
Hematology and blood chemistry	X[1]	X	X	X	X	X	X	X	X
Blood hormones	X[1]		X			X	X	X	X
Urinalysis	X[1]								X
Number of blood transfusions	X								

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LNP023 PK		X[2]		X[2]					
Adverse Events	As required								X
Concomitant meds/Therapies	As required								X
Comments	As required								X

* Eligibility needs to be confirmed before first dose of LNP023 is administered
S: Captured as Source Data only
[1] Pre-LNP023 and LFG316 dose
[2] Two time points: pre LNP023 morning dose and 2h post morning LNP023 dose
[3] B.i.d. administration
[4] Safety follow up call should happen approximately 1 month after last LNP023 dose is administered for patients that do not roll over into CLNP023C12001B
[5] Patient diary will be implement to collect information on missing LNP023 doses

8.1 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 incapable of doing so, in cases where the subject's representative gives consent, the subject should be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she should 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 (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source documents.

The date of signing of informed consent (and withdrawal, if later withdrawn) should be documented in the CRF.

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

If applicable, Pregnancy Outcome Reporting Consent for female patients will be implemented.

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In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or Ethics Committee approval will be obtained.

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

8.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects.

Relevant medical history/current medical conditions data includes data until signature of informed consent. Where possible, diagnoses and not symptoms will be recorded.

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

Historical data of serum LDH may be recorded, if available, to help characterize disease status and progression.

8.3 Safety

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

8.3.1 Physical examination

8.3.2 Vital signs

- Body temperature
- Blood pressure (BP)
- Pulse

Blood pressure and pulse should be collected in a sitting position, after the subject has been sitting for 3 minutes.

8.3.3 Height and weight

- Height
- Body weight (to be used for ongoing dose calculation according to SOM instructions)
- Body mass index (BMI) will be calculated (Body weight (kg) / [Height (m)]^2)

8.3.4 Laboratory evaluations

Clinically relevant deviations of laboratory test results that are considered unexpected in PNH patients, occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count will be measured.

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, triglycerides.

- 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.

- Blood hormones (For period 4 only):
  - Thyroid hormone levels including T3, T4, TSH and reversed T3.
  - Reproductive hormones: Testosterone, Dihydrotestosterone (DHT), Follicle stimulating hormone (FSH), Luteinizing hormone (LH)

Urinalysis

A semi-quantitative "dipstick" evaluation for the following parameters will be performed: specific gravity, pH, glucose, protein, bilirubin, urobilinogen, ketones, nitrite, leukocytes and blood/hemoglobin.

If the dipstick result is positive for protein, nitrite, leucocytes and/or blood the sample will be sent for microscopic analysis of WBC, RBC and casts.

8.3.5 Electrocardiogram (ECG)

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

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

8.3.6 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have regular serum pregnancy test at screening and urine pregnancy tests at all other time points during the study. A positive urine pregnancy test requires immediate interruption of study drug until serum β-hCG is performed and found to be negative. Only for post-menopausal women hormone measurement (FSH) to confirm post-menopausal status is required at screening.

8.3.7 Vaccination

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 meningococcal vaccine(s) should be administered at least two weeks prior to starting LFG316 and should be boosted during the study as per recommendation. If LNP023 treatment has to start earlier than 2 weeks post vaccination, prophylactic antibiotic treatment must be initiated.

For patients participating in period 4, vaccination for the prevention of *S. pneumoniae* and *H. influenzae* infections should be administered at least 2 weeks prior to first dosing with LNP023, as per local guidelines and regulations. If LNP023 treatment has to start earlier than 2 weeks post vaccination, prophylactic antibiotic treatment must be initiated. Based on local recommendations, revaccination at the start of LFG316 therapy should be considered for previously vaccinated subjects as well as during LFG316 and LNP023 therapy for subjects who will receive prolonged treatment.

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

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8.5 Pharmacokinetics

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

Further details on sample collection, numbering, processing and shipment can be found in the Site Operations Manual.

Determination of the concentration of total LFG316 in serum will be performed using an ELISA or LC/MS assay.

A detailed description of the method used to quantify the concentration of total LFG316 will be included in the bioanalytical raw data of the study and in the bioanalytical data report.

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

Total LFG316 concentrations will be expressed as µg/mL.

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PK samples remaining after completion of the determination of total LFG316 may be used for exploratory assessments or other bioanalytical purposes (e.g. cross check between different sites, stability assessment). Given the exploratory nature of the work, the analytical method used for those assessments will not be validated.

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

The following pharmacokinetic parameters will be determined (if feasible) using non-compartmental method(s) with Phoenix WinNonlin (Version 6.2 or higher): AUC (0-tlast), AUC(0-t), Cmax, tmax, Cmax/D, AUC/D. The linear trapezoidal rule will be used for AUC calculation.

For LNP023 a exposure assessment will be done by measuring LNP023 in plasma at predose as well as at 2 hr (apparent Cmax). Non-compartimental analysis will not be conducted to calculate any other PK parameters.

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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 or clinical investigation subject *after providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The occurrence of adverse events should 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, laboratory test, 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 related events are included in Section 9.3.

Adverse events must be recorded on the Adverse Events CRF pages for subjects that pass screening and enter into the study. The adverse events should be reported according to 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 (no/yes)
3. its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
4. whether it constitutes a serious adverse event (SAE) See Section 9.2 for definition of SAE

5. action taken regarding [study/investigational] treatment(select as appropriate).
   All adverse events should be treated appropriately. Treatment may include one or more of the following:
   - no action taken (i.e. further observation only)
   - study treatment dosage adjusted/temporarily interrupted
   - study treatment permanently discontinued due to this adverse event
   - concomitant medication given
   - non-drug therapy given
   - subject hospitalized/subject's hospitalization prolonged
6. its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it should 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 study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or Core Data Sheet (for marketed drugs) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed.

The investigator should 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 should be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

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 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 patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the subject or may require medical or surgical intervention.

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 more severe.

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

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

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 patient 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.

All AEs (serious and non-serious) are captured on the CRF, SAEs also require individual reporting to DS&E as per Section 9.2.2.

9.2.2 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the ***last study drug administration*** must be reported to Novartis within 24 hours of learning of its occurrence as described below. Any SAEs experienced after this should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (either initial or follow up information*)* is collected and recorded on the paper Serious Adverse Event Report Form. The investigator must assess the relationship to each specific component of study treatment (if study treatment consists of several drugs) 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, notifying the Clinical Trial Leader. Contact information is listed in the Site Operations Manual.

The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the source 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.

SAEs (initial and follow-up) that are recorded electronically in the Electronic Data Capture system should be entered, saved and e-signed within 24 hours of awareness of the SAE or changes to an existing SAE. These data will automatically be submitted to Novartis Drug Safety & Epidemiology immediately after investigator signature or 24 hours after entry, whichever occurs first. Study site personnel must also inform the Clinical Trial Leader.

Follow- up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should 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 investigational treatment a Drug Safety and Epidemiology 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 investigational 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.

9.3 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.

The following two categories of abnormalities / adverse events have to be considered during the course of the study:

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to Table 9-1 and Table 9-2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event should be followed up by the investigator or designated personal at the trial site, as summarized below and detailed in Table 9-2.

For the liver laboratory trigger:

- Repeating the LFT within the next week to confirm elevation

These LFT repeats should be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory should then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event should be reported on the Liver CRF pages.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug (refer to Section 7.1, if appropriate
- Hospitalization of the subject if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g. disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed should be recorded as appropriate in the CRF, including the liver event overview CRF pages.

Table 9-1 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers	3 x ULN < ALT / AST ≤ 5 x ULN
	1.5 x ULN < TBL ≤ 2 x ULN (unless TBL elevation is attributed to hemolysis, e.g. unconjugated fraction)
Liver events	ALT or AST > 5 × ULN
	ALP > 2 × ULN (in the absence of known bone pathology)
	TBL > 2 × ULN (in the absence of known Gilbert syndrome, unless elevation attributed to PNH hemolysis, e.g. unconjugated fraction)
	ALT or AST > 3 × ULN and INR > 1.5
	Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)
	Any clinical event of jaundice (or equivalent term)
	ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
	Any adverse event potentially indicative of a liver toxicity *

Table 9-2 Follow up requirements for liver events and laboratory triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Check if increase in TBL is due to rise in conjugated [direct] or unconjugated [indirect] fraction • If TBL elevation cannot be explained by hemolysis (e.g. unconjugated bilirubin, reticulocytes, haptoglobin), discontinue the study drug immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
ALT or AST		
> 8 × ULN	• Discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study drug immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for *more than 2 weeks*, discontinue the study drug • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit

Criteria	Actions required	Follow-up monitoring
TBL (isolated)		
> 3 × ULN or baseline, whichever is higher (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • Check if increase is due to rise in conjugated [direct] or unconjugated [indirect] fraction • If elevation cannot be explained by hemolysis (unconjugated bilirubin, reticulocytes, haptoglobin), discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Jaundice Unless attributed to PNH	• Discontinue the study drug immediately • Hospitalize the patient • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study drug interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

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

[a] Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN (if TBL within normal range at baseline) or TBL > 2 × baseline (if TBL was elevated at baseline), but without notable increase in ALP to > 2 × ULN

[b] (General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

[c] Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

9.4 Renal safety monitoring

Renal events are defined as one of the following:

- confirmed (after ≥ 24h) increase in serum creatinine of ≥ 25% compared to baseline during normal hydration status
- new onset (≥1+) proteinuria (that is not attributed to underlying disease, as judged by the investigator), hematuria or glucosuria; or as a
- doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable).

The following two categories of abnormalities/adverse events have to be considered during the course of the study:

- Serum creatinine triggers that will require follow up and repeat assessments of the abnormal laboratory parameter
- Urine dipstick triggers that will require follow up and repeat assessments of the abnormal laboratory parameter

Table 9-3 Specific renal alert criteria and actions

Renal Event	Actions
Serum creatinine increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Serum creatinine increase ≥ 50 % compared to baseline	Follow up within 24-48h if possible Consider drug interruption Consider patient hospitalization /specialized treatment
Albumin- or Protein-creatinine ratio increase ≥ 2-fold Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol; New dipstick proteinuria ≥ 1+ Protein-creatinine ratio (PCR)≥ 150 mg/g or >15 mg/mmol (unless proteinuria is attributable to underlying disease)	Confirm value after 24-48h Perform urine microscopy Consider drug interruption / discontinuation
New dipstick glucosuria ≥ 1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR
Document contributing factors: co-medication, other co-morbid conditions, and additional diagnostic procedures performed in the CRF	
Monitor patient regularly (frequency at investigator's discretion) until one of the following: Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline) 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.	

9.5 Pregnancy reporting

To ensure patient safety, each pregnancy in a subject on study drug 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. 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 must be recorded on a Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on an SAE Report Form.

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.

The Sponsor will advise all the participating the Investigators 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 CRFs 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 entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to 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. Additionally, a central analytics organization may analyse data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or

assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the eligibility 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 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 a CD-ROM or paper 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 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.

CRO staff working on behalf of Novartis review the data entered into the eCRFs 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 the CRO working on behalf of Novartis who will make the correction to the database.

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).

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10.3 Data Monitoring Committee

Not required.

10.4 Adjudication Committee

Not required.

11 Data analysis

11.1 Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received. The study has four parts, and the safety and efficacy analysis will be presented for period 1, period 2 and period 3 combined, and separately for period 4.

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

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

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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 and summarized.

11.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

Data for study drug administration, and concomitant therapies will be listed and summarized.

11.4 Analysis of the primary variable(s)

The primary objective of this study is to assess the effect of LFG316 on the reduction of intravascular hemolysis in PNH patients as assessed by reduction in serum LDH levels after the first 4 weeks of treatment and during the entire treatment period.

11.4.1 Variable(s)

The primary efficacy variable for assessing the effect of LFG316 over the first 4 weeks of treatment is response rate where a patient will be considered a responder if the percentage reduction from baseline in serum LDH is at least 60% at any time up to and including week 4 for that patient.

The primary efficacy variable for assessing the effect of LFG316 over the entire treatment period is the actual serum LDH value measured at multiple time points during the study.

11.4.2 Statistical model, hypothesis, and method of analysis

Proof of concept will be based on LDH levels during the first four weeks. A positive sign of efficacy is when:

- The estimated median response rate is at least 50%

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For the analysis of serum LDH values from multiple time points, a longitudinal model analysis of log-transformed LDH levels over time pre- and post-treatment will also be performed.

Longitudinal modelling will include individual and treatment average graphical presentations over time incorporating any historical LDH data collected so as to better put post-treatment changes in context.

11.4.3 Handling of missing values/censoring/discontinuations

The study aims to replace subjects enrolled before protocol amendment 5 who discontinue before the end of period 1 for reasons other than safety and the primary responder analysis will be based on period 1 completers only, in a per protocol fashion.

Further longitudinal model analyses performed to assess the effect of missing data on the conclusions drawn from the primary analysis will include, if available, data from any subjects who discontinued early. Lack of efficacy will not be considered a missing value. Even if treatment is discontinued, LDH values should still be assessed in the eight-week follow-up period.

11.4.4 Supportive analyses

For comparison with the Bayesian analysis above, supportive analyses are in the frequentist paradigm giving the possibility of incorporating meaningful prognostic characteristics, such as being carriers or not of the minor allelic variant of C5, in modelling the response rate as binary data in logit models.

Alternative longitudinal model analyses of log-transformed LDH levels over time pre- and post-treatment may also be performed, to assess the sensitivity of the primary analysis to missing data, any deviations from assumptions, and to also assess the impact of prognostic factors on conclusions. Commercially Confidential Information

Additionally serum LDH at each timepoint will also be summarized in terms of the number and percentage of patients achieving a reduction in LDH to within the normal limits.

11.5 Analysis of secondary CCI variables

The analysis of the two secondary endpoints of standard safety monitoring with increased vigilance for infections and measurement of serum concentrations of LFG316 are covered in Section 9.1 (adverse events) and Section 8.5 (pharmacokinetics) respectively. There will be no adjustment for multiplicity over the three main analyses of efficacy (primary), safety and PK (both secondary).

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11.5.1 Efficacy / CCI

The analysis of the primary efficacy endpoint of reduction in LDH is described above in Section 11.4.2 and Section 11.4.4.

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11.5.2 Safety

Adverse events

All information obtained on adverse events will be displayed as summary and by subject as per the secondary objective.

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.

As this study has four treatment periods an adverse event starting in period 1 and continuing into the next period is counted only in the period 1. A subject with multiple adverse events within a body system and treatment period is only counted once towards the total of this body system and treatment period. There will be three summaries of AEs, at the end of treatment period 1; periods 2 and 3 combined; and period 4.

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.

11.5.3 Pharmacokinetics

Total LFG316 concentration data will be listed by subject, and visit/sampling time point. Descriptive summary statistics will be provided by visit/sampling time point, CCI

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

Pharmacokinetic parameters will be calculated as described in Section 8.5 and will be listed by subject.

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11.5.5 Other assessments

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11.6 Sample size calculation

The sample size text below still applies following amendment 6, as the potential increase in number of patients treated is not so much to increase power of the study but to provide a treatment option for C5 variant PNH patients without an alternative. Notwithstanding that, if further patients are recruited then overall power will increase and the calculations below may then also be applicable to C5-variant patients only. If no further patients are recruited, the below text remains valid.

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11.7 Power for analysis of key secondary variables

Not applicable.

11.8 Interim analyses

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12 Ethical considerations

12.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented 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 should 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 around 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

Novartis assures that 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 (e.g. peer-reviewed journal) and/or posted in a publicly accessible database of clinical trial results.

13 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study patients. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

Investigators must apply due diligence to avoid protocol deviations. If the 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/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

13.1 Protocol Amendments

Any change or addition 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.

Only amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented, provided the Health Authorities and the reviewing IRB/IEC are subsequently notified by protocol amendment.

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 CTL should be informed and (serious) adverse event reporting requirements (Section 9) followed as appropriate.

14 References

Available upon request.

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