Clinical trial results:
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)

Summary

EudraCT number	2014-005338-74
Trial protocol	CZ LT
Global end of trial date	24 May 2022

Results information

Result version number	v1
This version publication date	08 June 2023
First version publication date	08 June 2023

Trial information

Trial identification

Sponsor protocol code	CLFG316X2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02534909
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Study Director, Novartis Pharmaceuticals, 1 862 778-8300, novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 February 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of LFG316 on the reduction of intravascular hemolysis in PNH patients.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy:

This was an open-label, non-controlled study in patients with PNH, enrolling 10 patients and consisting of a screening period and 4 treatment periods as follows:
A 60-day screening period was used to assess eligibility and to conduct vaccinations if required. Patients who met the eligibility criteria at screening entered treatment period 1 for baseline evaluation and received LFG316 infusion every 14 days for 4 weeks.

Following assessment of efficacy (hemolytic activity by serum LDH) at the end of treatment period 1, patients entered the optional 48-week treatment period 2 and continued LFG316 infusions every 14 days. At the end of treatment period 2, LFG316-responsive patients (assessed based on the investigator's judgment) were allowed to enter an additional extension period of up to 260 weeks (treatment period 3) in which they continued to receive LFG316 every 14 days. Period 4, which allowed patients to switch to LNP023, lasted approximately 21 weeks. During the first 4 weeks, patients continued to receive LFG316 in addition to oral administration of LNP023. After 4 weeks, patients discontinued LFG316 and continued with LNP023 monotherapy for approximately 16 weeks (± 28 days). Patients who participated in period 4 could join the long-term extension study CLNP023C12001B as soon as their eligibility was confirmed and study CLNP023C12001B was open to receive patients. There was no LNP023 treatment gap between the studies.

Evidence for comparator:

This study used an open-label, single treatment design.

Actual start date of recruitment	09 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 7
Country: Number of subjects enrolled	Czechia: 2
Country: Number of subjects enrolled	Lithuania: 1
Worldwide total number of subjects	10
EEA total number of subjects	3

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	9
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

10 participants were enrolled at 7 sites in 3 countries.

Pre-assignment

Screening details:

The study had a 60-day screening period to assess eligibility.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	LFG316 then LNP023

Arm description:

LFG316: Treatment periods 1-3 and first 4 weeks of period 4. LNP023: Treatment Period 4

Arm type	Experimental
Investigational medicinal product name	LFG316 then LNP023
Investigational medicinal product code	LFG316 then LNP023
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

In treatment periods 1 to 3, patients received the following:

LFG316 20 mg/kg as i.v. infusion every 2 weeks
Patients participating in treatment period 4 received the following:

LFG316 20 mg/kg as i.v. infusion every 2 weeks for 4 weeks (total 2 infusions)

LNP023 200 mg b.i.d. for approximately 20 weeks. Four capsules (each 50 mg) were administered each time study medication was taken.

Number of subjects in period 1	LFG316 then LNP023
Started	10
Completed	9
Not completed	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups	
Reporting group title	LFG316 then LNP023
Reporting group description:	
LFG316: Treatment periods 1-3 and first 4 weeks of period 4. LNP023: Treatment Period 4	

Reporting group values	LFG316 then LNP023	Total	
Number of subjects	10	10	
Age Categorical			
Adult study. No peds			
Units: Participants			
<=18 years	0	0	
Between 18 and 65 years	9	9	
>=65 years	1	1	
Age Continuous			
Average age of participants			
Units: years			
arithmetic mean	43.0		
standard deviation	± 11.68	-	
Sex: Female, Male			
Sex			
Units: Participants			
Female	4	4	
Male	6	6	
Race/Ethnicity, Customized			
Race			
Units: Subjects			
Caucasian	3	3	
Asian	7	7	

End points

End points reporting groups

Reporting group title	LFG316 then LNP023
Reporting group description:	
LFG316: Treatment periods 1-3 and first 4 weeks of period 4. LNP023: Treatment Period 4	

Primary: Number of Responders of reduction in serum lactate dehydrogenase (LDH) levels within the first 4 weeks

End point title	Number of Responders of reduction in serum lactate dehydrogenase (LDH) levels within the first 4 weeks[1]
End point description:	
A patient was considered a responder if the percentage reduction from baseline (average of all predose measurements) in serum LDH was at least 60% at any time up to and including Week 4 for that patient	
End point type	Primary
End point timeframe:	
Up to the first 4 weeks in period 1	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed for this outcome.

End point values	LFG316 then LNP023			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Participants				
Responder	10			
Non-responder	0			
LDH within minimal range	6			

Statistical analyses

No statistical analyses for this end point

Primary: Bayesian analysis for the primary endpoint: response rate

End point title	Bayesian analysis for the primary endpoint: response rate[2]
End point description:	
Bayesian analysis was performed as a proof of concept for the primary efficacy analysis. The Bayesian analysis provides statistical evidence for the reduction in serum LDH concentrations during the first 4 weeks of treatment with LFG316 because the probability that the true median response rate is ≥ 50% is more than 95%	
End point type	Primary
End point timeframe:	
Up to the first 4 weeks in period 1	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed for this outcome.

End point values	LFG316 then LNP023			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: Median Response Rate				
median (confidence interval 95%)	99.0 (81.9 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage change in serum lactate dehydrogenase (LDH) levels over the entire treatment period from baseline

End point title	Percentage change in serum lactate dehydrogenase (LDH) levels over the entire treatment period from baseline[3]

End point description:

Change in serum lactate dehydrogenase (LDH) levels over the entire treatment period after treatment with LFG316 from baseline

End point type	Primary

End point timeframe:

Period 1 Day 29, Period 2 Day 365, Period 3 Day 1429, Period 4 Day 141

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed for this outcome.

End point values	LFG316 then LNP023			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percentage chznge from baseline				
arithmetic mean (standard deviation)				
Period 1 Day 29	-78.35 (± 11.190)			
Period 2 Day 365	-78.56 (± 11.550)			
Period 3 Day 1429	-81.65 (± 8.135)			
Period 4 Day 141	-78.69 (± 9.288)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Concentration (Tmax) - Pharmacokinetics parameter

End point title	Time to Maximum Concentration (Tmax) - Pharmacokinetics parameter

End point description:

Blood draw for pharmacokinetics evaluation after treatment with LFG316.

Pharmacokinetic parameters were determined using non-compartmental methods based on LFG316 concentrations in serum.

End point type	Secondary

End point timeframe:

Period 1 Day 1

End point values	LFG316 then LNP023			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: hours				
median (full range (min-max))	2.56 (2.05 to 3.10)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUC (0-t) = Area under the serum concentration of LFG316 versus time curve from time zero (pre-dose) to time of last quantifiable concentration (0-t) - Pharmacokinetics parameter.

End point title	AUC (0-t) = Area under the serum concentration of LFG316 versus time curve from time zero (pre-dose) to time of last quantifiable concentration (0-t) - Pharmacokinetics parameter.

End point description:

Blood draw for pharmacokinetics evaluation after treatment with LFG316. Pharmacokinetic parameters were determined using non-compartmental methods based on LFG316 concentrations in serum.

End point type	Secondary

End point timeframe:

Period 1 Day 1

End point values	LFG316 then LNP023			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: h*µg/mL				
arithmetic mean (standard deviation)	73700 (± 12600)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) - Pharmacokinetics parameter

End point title	Maximum Plasma Concentration (Cmax) - Pharmacokinetics parameter

End point description:

Blood draw for pharmacokinetics evaluation after treatment with LFG316.

Pharmacokinetic parameters were determined using non-compartmental methods based on LFG316 concentrations in serum.

End point type	Secondary

End point timeframe:

Day 1 Period 1

End point values	LFG316 then LNP023			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: µg/mL				
arithmetic mean (standard deviation)	407 (± 69.2)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment (Day 1) up to 4 weeks after last dose (Day 2213) in participants transitioning to Period 4 and up to 8 weeks after last dose (Day 2241) in participants ending participation after Period 3.

Adverse event reporting additional description:

Adverse events (AEs) are any sign or symptom that occurs during the conduct of the trial and safety follow-up. Adverse events (AEs) are any sign or symptom that occurs during the treatment period and safety follow-up.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	LFG316 Periods 1 to 3

Reporting group description:

LFG316 20 mg in Periods 1 to 3

Reporting group title	Total

Reporting group description:

Total

Reporting group title	LFG316 + LNP023 Period 4

Reporting group description:

LFG316 20 mg + LNP023 200 mg Period 4 Patients received the combination during the initial 4 weeks and then they discontinued LGF316 and continued with LNP023 monotherapy.

Serious adverse events	LFG316 Periods 1 to 3	Total	LFG316 + LNP023 Period 4
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 10 (30.00%)	3 / 10 (30.00%)	0 / 9 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0		
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis viral			

subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngitis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	LFG316 Periods 1 to 3	Total	LFG316 + LNP023 Period 4
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	10 / 10 (100.00%)	6 / 9 (66.67%)
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Hypertension			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Oedema peripheral			

subjects affected / exposed	2 / 10 (20.00%)	2 / 10 (20.00%)	0 / 9 (0.00%)
occurrences (all)	2	2	0
Pyrexia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Immune system disorders			
Immunisation reaction			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Erectile dysfunction			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Epistaxis			
subjects affected / exposed	2 / 10 (20.00%)	2 / 10 (20.00%)	0 / 9 (0.00%)
occurrences (all)	2	2	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Sleep disorder			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 10 (20.00%)	2 / 10 (20.00%)	0 / 9 (0.00%)
occurrences (all)	2	2	0
International normalised ratio decreased			

subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
International normalised ratio increased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Platelet count increased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Pulmonary function test decreased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Contusion			
subjects affected / exposed	2 / 10 (20.00%)	2 / 10 (20.00%)	0 / 9 (0.00%)
occurrences (all)	2	2	0
Meniscus injury			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Peripheral nerve injury			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Shunt stenosis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Thermal burn			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Tooth fracture			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Wound			

subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Congenital, familial and genetic disorders			
Brugada syndrome			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Atrioventricular block first degree			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 10 (50.00%)	5 / 10 (50.00%)	1 / 9 (11.11%)
occurrences (all)	5	5	0
Migraine			
subjects affected / exposed	2 / 10 (20.00%)	2 / 10 (20.00%)	0 / 9 (0.00%)
occurrences (all)	2	2	0
Migraine with aura			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Blood and lymphatic system disorders			
Thrombocytosis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Neutropenia			
subjects affected / exposed	2 / 10 (20.00%)	2 / 10 (20.00%)	0 / 9 (0.00%)
occurrences (all)	2	2	0
Leukopenia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Haemolysis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0

Anaemia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	2 / 10 (20.00%)	2 / 10 (20.00%)	0 / 9 (0.00%)
occurrences (all)	2	2	0
Gastrointestinal disorders			
Enteritis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Enterocolitis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Gastritis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Gastritis erosive			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Mouth haemorrhage			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Nausea			
subjects affected / exposed	3 / 10 (30.00%)	3 / 10 (30.00%)	0 / 9 (0.00%)
occurrences (all)	3	3	0
Stomatitis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Toothache			
subjects affected / exposed	2 / 10 (20.00%)	2 / 10 (20.00%)	0 / 9 (0.00%)
occurrences (all)	2	2	0
Diarrhoea			

subjects affected / exposed	2 / 10 (20.00%)	2 / 10 (20.00%)	0 / 9 (0.00%)
occurrences (all)	2	2	0
Dental caries			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Colitis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Abdominal pain upper			
subjects affected / exposed	2 / 10 (20.00%)	2 / 10 (20.00%)	0 / 9 (0.00%)
occurrences (all)	2	2	0
Abdominal pain			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Duodenal ulcer			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Skin and subcutaneous tissue disorders			
Haemorrhage subcutaneous			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Dry skin			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Dermatitis			
subjects affected / exposed	2 / 10 (20.00%)	2 / 10 (20.00%)	0 / 9 (0.00%)
occurrences (all)	2	2	0
Seborrhoeic dermatitis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Rash maculo-papular			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Rash			
subjects affected / exposed	2 / 10 (20.00%)	2 / 10 (20.00%)	0 / 9 (0.00%)
occurrences (all)	2	2	0

Pruritus			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Haematuria			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Nephrolithiasis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Proteinuria			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Renal colic			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Renal cyst			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 10 (20.00%)	2 / 10 (20.00%)	0 / 9 (0.00%)
occurrences (all)	2	2	0
Back pain			
subjects affected / exposed	3 / 10 (30.00%)	3 / 10 (30.00%)	0 / 9 (0.00%)
occurrences (all)	3	3	0
Osteochondrosis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Pain in extremity			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	1 / 9 (11.11%)
occurrences (all)	1	1	0
Infections and infestations			

Cellulitis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Cystitis			
subjects affected / exposed	4 / 10 (40.00%)	4 / 10 (40.00%)	0 / 9 (0.00%)
occurrences (all)	4	4	0
Gastroenteritis			
subjects affected / exposed	3 / 10 (30.00%)	3 / 10 (30.00%)	0 / 9 (0.00%)
occurrences (all)	3	3	0
Helicobacter infection			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Herpes simplex			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Herpes zoster			
subjects affected / exposed	3 / 10 (30.00%)	3 / 10 (30.00%)	0 / 9 (0.00%)
occurrences (all)	3	3	0
Lyme disease			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Nasopharyngitis			
subjects affected / exposed	8 / 10 (80.00%)	8 / 10 (80.00%)	0 / 9 (0.00%)
occurrences (all)	8	8	0
Paronychia			
subjects affected / exposed	2 / 10 (20.00%)	2 / 10 (20.00%)	0 / 9 (0.00%)
occurrences (all)	2	2	0
Pharyngitis			
subjects affected / exposed	2 / 10 (20.00%)	2 / 10 (20.00%)	0 / 9 (0.00%)
occurrences (all)	2	2	0
Respiratory tract infection			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0
Respiratory tract infection viral			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	0 / 9 (0.00%)
occurrences (all)	1	1	0

Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0
Metabolism and nutrition disorders Dehydration subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0
Hyperferritinaemia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 May 2015	The main purpose of this amendment was to address a Health Authority request to amend inclusion criterion #7. The amendment specified that treatment with LFG316 may only be initiated at the earliest 2 weeks after meningococcal vaccination. The previous wording allowed the administration of study drug immediately after vaccination, provided that prophylactic antibiotics were used for at least 2 weeks. Other changes included clarifications and changes to wording, and minor corrections and corrections for typographical errors.
23 June 2015	The main purpose of this amendment was to address a request from the Health Authority of the Czech Republic to lower the maximum age of patients eligible for participation in this clinical study from 75 to 65 years of age in the Czech Republic. A requirement for close medical supervision at the study site during the infusion time of LFG316 and up to 2 hours after the end of the infusion during Treatment Period 1 was included.
30 June 2015	The main purpose of this amendment was to address clarification requests from the Health Authority of Japan with regards to vaccination requirements, safety follow-up, and safety measures in case of specific adverse events (e.g., infusion reactions).
21 October 2015	The main purpose of this amendment was to extend the screening period from 28 to 60 days to enable and comply with local recommendations for vaccination whenever available and if deemed necessary at investigator's discretion. Inclusion Criterion #2 was modified by removing the time limit from the moment of diagnosis of PNH (i.e., 6 months). Based on the chronicity of the disease, the certainty of the diagnosis, and investigators feedback, the 6 months were not deemed necessary to define eligibility of the patients. Clarifications on Exclusion Criterion #09 and #10 were added. Minor corrections and clarifications were made.
15 June 2016	The main purpose of this amendment was to ensure a seamless continuation of treatment in LFG316-responsive patients already enrolled in the study, and to continue to assess long term safety, efficacy, pharmacokinetic and pharmacodynamic data beyond 48 weeks. The study design was updated with the addition of extension period 3. Additional changes were made to reduce patients' burden and to clarify exclusion criteria.

21 September 2017	The main purpose of this amendment was to allow recruitment of up to approximately five additional PNH patients who were refractory to eculizumab therapy due to a genetic variant leading to amino acid exchange (Arg885His) in the C5 protein, due to a lack of effective treatment options in this subpopulation of PNH patients. The upper age limit was removed to allow older variant patients to participate in the study. 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 treatment of older PNH patients. As there were no safety concerns in study CLFG316B2102 in healthy volunteers infused over 30 and 60 minutes, it was considered appropriate to decrease the required infusion time in Periods 2 and 3 from approximately 2 hours to a minimum of 40 minutes.
05 March 2019	The main purpose of this amendment was to stop the recruitment into the trial, and to extend the study treatment for currently enrolled patients beyond the 3rd year in period 3. The assessment schedule reflects a reduced number of study visits and assessments during the extended period 3 with focus on safety assessments as the reason for this amendment is to secure extended LFG316 treatment access for patients currently enrolled in the trial. In addition, updated guidance about consent, withdrawal and early study termination is provided.
15 December 2020	The main purpose of this amendment was to convert ongoing study patients from LFG316 to LNP023, a potent, selective and reversible low molecular weight Factor B (FB) inhibitor for oral administration and allow them to be considered for participation in an open label extension study with LNP023 (CLNP023C12001B). Treatment period 4 was implemented to convert patients with PNH receiving i.v. LFG316 to oral LNP023. As per strategic decision, further development of LFG316 was terminated in favor of LNP023, Novartis offered patients enrolled in study CLFG316X2201 a conversion from LFG316 to LNP023, aiming to provide uninterrupted treatment for these PNH patients. With a protocol amendment, study Period 4 was implemented to allow patients to first convert from LFG316 to LNP023 therapy and then to join the separate LNP023 roll-over extension study CLNP023C12001B.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

LFG316 development was terminated in favor of LNP023. CLFG316X2201 patients were offered conversion from LFG316 to LNP023 for uninterrupted treatment.

Notes: