EU Clinical Trials Register

Clinical trial results:

A randomized, multicenter, active-comparator controlled, open-label trial to evaluate efficacy and safety of oral, twice daily LNP023 in adult patients with PNH and residual anemia, despite treatment with an intravenous anti-C5 antibody.

Summary

EudraCT number	2019-004665-40
Trial protocol	FR DE HU CZ NL IT
Global end of trial date	06 March 2023

Results information

Result version number	v2 (current)
This version publication date	21 March 2024
First version publication date	05 October 2023
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CLNP023C12302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04558918
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office , Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com
Scientific contact	Clinical Disclosure Office , Novartis Pharma AG, 41 613241111, 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	06 March 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate superiority of iptacopan compared to anti-C5 antibody treatment in the proportion of patients achieving hematological response. Two hematological responder endpoints were defined as primary endpoints:
• Increase from baseline Hb levels ≥ 2 g/dL (assessed between Day 126 and Day 168) in the absence of RBC transfusion between Day 14 and Day 168.
• Hb levels ≥ 12 g/dL (assessed between Day 126 and Day 168) in the absence of RBC transfusion between Day 14 and Day 168.

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: -

Evidence for comparator: -

Actual start date of recruitment	25 January 2021
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	Brazil: 4
Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Germany: 20
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	Japan: 9
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	97
EEA total number of subjects	61

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)	71
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in 39 investigative sites in 12 countries: Netherlands(1), Germany(5), France(3), Japan(7), Korea, Republic of(1), Italy(7), Spain(3), Taiwan(2), United Kingdom(2), Czech Republic(1), United States(5), Brazil(2)

Pre-assignment

Screening details:

Vaccination against Neisseria meningitidis, Streptococcus pneumoniae and Haemophilus influenzae infections was required prior to the start of treatment, if the patient had not been previously vaccinated, or if a booster was required.

Period 1

Period 1 title	Randomized treatment period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	LNP023 200mg b.i.d.

Arm description:

Iptacopan 200mg b.i.d. hard gelatin capsule. After 24 weeks of LNP023 200mg b.i.d. treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive an additional 24 weeks of LNP023 200mg b.i.d.

Arm type	Experimental
Investigational medicinal product name	ptacopan
Investigational medicinal product code	LNP023
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

LNP023 200mg b.i.d.

Arm title	Anti-C5 antibody

Arm description:

In the Randomized Treatment Period patients randomized to receive Anti-C5 antibody continued with the same stable regimen of Anti-C5 antibody therapy as they had received prior to randomization. For eculizumab (administered as intravenous infusion every 2 weeks), the maintenance dose was a fixed dose, whereas for ravulizumab (administered as intravenous infusion every 8 weeks), the maintenance dose was based on body weight. After 24 weeks of Anti-C5 antibody treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive 24 weeks of LNP023 200mg b.i.d.

Arm type	Active comparator
Investigational medicinal product name	Ravulizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ravulizumab 300mg/30mL intravenousinfusion

Investigational medicinal product name	Eculizumab
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Eculizumab 300
mg/30mLconcentrate
solution forinfusion

Number of subjects in period 1	LNP023 200mg b.i.d.	Anti-C5 antibody
Started	62	35
Completed	62	35

Period 2

Period 2 title	Extension treatment period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	LNP023 200mg b.i.d.

Arm description:

Iptacopan 200mg b.i.d. hard gelatin capsule. After 24 weeks of LNP023 200mg b.i.d. treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive an additional 24 weeks of LNP023 200mg b.i.d.

Arm type	Experimental
Investigational medicinal product name	Iptacopan
Investigational medicinal product code	LNP023
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

LNP023 200mg b.i.d.

Arm title	Anti-C5 antibody

Arm description:

In the Randomized Treatment Period patients randomized to receive Anti-C5 antibody continued with the same stable regimen of Anti-C5 antibody therapy as they had received prior to randomization. For eculizumab (administered as intravenous infusion every 2 weeks), the maintenance dose was a fixed dose, whereas for ravulizumab (administered as intravenous infusion every 8 weeks), the maintenance dose was based on body weight. After 24 weeks of Anti-C5 antibody treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive 24 weeks of LNP023 200mg b.i.d.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2[1]	LNP023 200mg b.i.d.	Anti-C5 antibody
Started	61	34
Completed	61	34

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Of the 97 patients completing the Randomized Treatment Period, 95 entered the treatment extension period. One patient, initially randomized to anti-C5, did not enter the extension period.

Baseline characteristics

Reporting groups

Reporting group title	LNP023 200mg b.i.d.

Reporting group description:

Iptacopan 200mg b.i.d. hard gelatin capsule. After 24 weeks of LNP023 200mg b.i.d. treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive an additional 24 weeks of LNP023 200mg b.i.d.

Reporting group title	Anti-C5 antibody

Reporting group description:

In the Randomized Treatment Period patients randomized to receive Anti-C5 antibody continued with the same stable regimen of Anti-C5 antibody therapy as they had received prior to randomization. For eculizumab (administered as intravenous infusion every 2 weeks), the maintenance dose was a fixed dose, whereas for ravulizumab (administered as intravenous infusion every 8 weeks), the maintenance dose was based on body weight. After 24 weeks of Anti-C5 antibody treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive 24 weeks of LNP023 200mg b.i.d.

Reporting group values	LNP023 200mg b.i.d.	Anti-C5 antibody	Total
Number of subjects	62	35	97
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	44	27	71
From 65-84 years	18	8	26
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	51.7	49.8	
standard deviation	± 16.94	± 16.69	-
Sex: Female, Male			
Units: participants			
Female	43	24	67
Male	19	11	30
Race/Ethnicity, Customized			
Units: Subjects			
White	48	26	74
Black or African American	2	2	4
Asian	12	7	19

Subject analysis sets

Subject analysis set title	Combined full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

Includes all patients randomized to LNP023 200 mg b.i.d and all patientsrandomized to anti-C5 treatment and who switched to LNP023 in the treatment extension period.

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

includes all patients to whom study treatment has been assigned by randomization

Reporting group values	Combined full analysis set	Full Analysis Set	
Number of subjects	96	97	
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age Continuous			
Units: years			
arithmetic mean	0.11		
standard deviation	±	±	
Sex: Female, Male			
Units: participants			
Female			
Male			
Race/Ethnicity, Customized			
Units: Subjects			
White			
Black or African American			
Asian			

End points

End points reporting groups

Reporting group title	LNP023 200mg b.i.d.

Reporting group description:

Iptacopan 200mg b.i.d. hard gelatin capsule. After 24 weeks of LNP023 200mg b.i.d. treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive an additional 24 weeks of LNP023 200mg b.i.d.

Reporting group title	Anti-C5 antibody

Reporting group description:

In the Randomized Treatment Period patients randomized to receive Anti-C5 antibody continued with the same stable regimen of Anti-C5 antibody therapy as they had received prior to randomization. For eculizumab (administered as intravenous infusion every 2 weeks), the maintenance dose was a fixed dose, whereas for ravulizumab (administered as intravenous infusion every 8 weeks), the maintenance dose was based on body weight. After 24 weeks of Anti-C5 antibody treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive 24 weeks of LNP023 200mg b.i.d.

Reporting group title	LNP023 200mg b.i.d.

Reporting group description:

Iptacopan 200mg b.i.d. hard gelatin capsule. After 24 weeks of LNP023 200mg b.i.d. treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive an additional 24 weeks of LNP023 200mg b.i.d.

Reporting group title	Anti-C5 antibody

Reporting group description:

In the Randomized Treatment Period patients randomized to receive Anti-C5 antibody continued with the same stable regimen of Anti-C5 antibody therapy as they had received prior to randomization. For eculizumab (administered as intravenous infusion every 2 weeks), the maintenance dose was a fixed dose, whereas for ravulizumab (administered as intravenous infusion every 8 weeks), the maintenance dose was based on body weight. After 24 weeks of Anti-C5 antibody treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive 24 weeks of LNP023 200mg b.i.d.

Subject analysis set title	Combined full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

Includes all patients randomized to LNP023 200 mg b.i.d and all patientsrandomized to anti-C5 treatment and who switched to LNP023 in the treatment extension period.

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

includes all patients to whom study treatment has been assigned by randomization

Primary: Marginal proportion (expressed as percentages) of participants with sustained increase in hemoglobin levels from baseline of ≥ 2 g/dL in the absence of red blood cell transfusions

End point title	Marginal proportion (expressed as percentages) of participants with sustained increase in hemoglobin levels from baseline of ≥ 2 g/dL in the absence of red blood cell transfusions

End point description:

Sustained increase in hemoglobin levels (responder) is defined as an increase from baseline in hemoglobin levels ≥ 2 g/dL on three out of four measurements taken at the visits occurring in last six weeks (between Day 126 and 168) of the randomized treatment period, without requiring red blood cell (RBC) transfusions between Day 14 and Day 168. Requiring RBC transfusions refers to any patient receiving transfusions or meeting protocol defined criteria (Hemoglobin level ≤ 9 g/dL with signs /and or symptoms of sufficient severity to warrant a transfusion or Hemoglobin of ≤ 7 g/dL, regardless of presence of clinical signs and/or symptoms).
The term 'marginal proportion' can be interpreted as the population average probability of being a responder for each treatment group. These values include adjustment for baseline covariates and missing data has also been taken into account.

End point type	Primary

End point timeframe:

Baseline, hemoglobin between Day 126 and Day 168 and absence of transfusions between Day 14 and Day 168

End point values	LNP023 200mg b.i.d.	Anti-C5 antibody		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	35		
Units: Percentage of responders				
number (confidence interval 95%)	82.3 (73.4 to 90.2)	2.0 (1.1 to 4.0)		

Statistical analyses

Statistical analysis title	Increase in hemoglobin levels
Comparison groups	LNP023 200mg b.i.d. v Anti-C5 antibody
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in marginal proportion
Point estimate	80.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	71.2
upper limit	87.6

Statistical analysis title	Increase in hemoglobin levels
Comparison groups	LNP023 200mg b.i.d. v Anti-C5 antibody
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	338.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	25.07
upper limit	4564.14

Notes:

[1] - two sided unadjusted p-value

Primary: Marginal proportion (expressed as percentages) of participants with sustained hemoglobin levels of ≥ 12 g/dL in the absence of red blood cell transfusions

End point title	Marginal proportion (expressed as percentages) of participants with sustained hemoglobin levels of ≥ 12 g/dL in the absence of red blood cell transfusions

End point description:

Sustained hemoglobin levels (responder) is defined as hemoglobin levels ≥ 12 g/dL on three out of four measurements taken at the visits occurring in last six weeks (between Day 126 and 168) of the randomized treatment period, without requiring red blood cell (RBC) transfusions between Day 14 and Day 168. Requiring RBC transfusions refers to any patient receiving transfusions or meeting protocol defined criteria (Hemoglobin level ≤ 9 g/dL with signs /and or symptoms of sufficient severity to warrant a transfusion or Hemoglobin of ≤ 7 g/dL, regardless of presence of clinical signs and/or symptoms). The term 'marginal proportion' can be interpreted as the population average probability of being a responder for each treatment group. These values include adjustment for baseline covariates and missing data has also been taken into account.

End point type	Primary

End point timeframe:

Hemoglobin between Day 126 and Day 168 and absence of transfusions between Day 14 and Day 168

End point values	LNP023 200mg b.i.d.	Anti-C5 antibody		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	35		
Units: Percentage of responders				
number (confidence interval 95%)	68.8 (58.4 to 78.9)	1.8 (0.9 to 4.0)		

Statistical analyses

Statistical analysis title	Increase in hemoglobin levels
Comparison groups	LNP023 200mg b.i.d. v Anti-C5 antibody
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Diff. in marginal proportion
Point estimate	67
Confidence interval	
level	95 %
sides	2-sided
lower limit	56.4
upper limit	76.9

Statistical analysis title	Increase in hemoglobin levels
Comparison groups	LNP023 200mg b.i.d. v Anti-C5 antibody

Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	495.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	24.41
upper limit	10066.53

Notes:

[2] - two sided unadjusted p-value

Primary: Percentage of patients meeting hematological response criterion after the start of LNP023 treatment

End point title	Percentage of patients meeting hematological response criterion after the start of LNP023 treatment[3]

End point description:

Patients with hematological response are those with ≥ 2g/dL increase in hemoglobin from baseline regardless of transfusions and patients with Hb ≥ 12g/dL regardless of transfusions.
Patients in the LNP023-LNP023 group received iptacopan from Day 1 to Day 336 (48 weeks) while patients in the anti-C5 antibody-LNP023 group received iptacopan from Day 169 to Day 336 (treatment extension period - 24 weeks).

End point type	Primary

End point timeframe:

Up to 48 weeks

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 planned for this primary outcome.

End point values	LNP023 200mg b.i.d.	Anti-C5 antibody		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	34		
Units: Percentage of participants				
number (not applicable)				
≥2 g/dL increase in Hb from baseline	86.4	72.4		
Hb ≥12 g/dL	67.8	58.6		

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in Hemoglobin at Visit Day 336

End point title	Change from baseline in Hemoglobin at Visit Day 336

End point description:

Patients randomized to anti-C5 treatment switched to LNP023 (iptacopan) on Day 169 and were treated until Day 336 (treatment extension period).

End point type	Primary
End point timeframe:	
Baseline, Day 336	

End point values	LNP023 200mg b.i.d.	Anti-C5 antibody		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	30		
Units: g/dL				
arithmetic mean (confidence interval 95%)	3.35 (3.04 to 3.67)	3.36 (2.94 to 3.79)		

Statistical analyses

Statistical analysis title	Change from baseline in hemoglobin at day 336
Comparison groups	LNP023 200mg b.i.d. v Anti-C5 antibody
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Adjusted mean difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	0.51

Primary: Number of patients not requiring RBC transfusions after the start of LNP023 treatment

End point title	Number of patients not requiring RBC transfusions after the start of LNP023 treatment[4]
End point description:	

Requiring RBC transfusions refers to any patient receiving transfusions or meeting protocol defined criteria (Hemoglobin level ≤ 9 g/dL with signs /and or symptoms of sufficient severity to warrant a transfusion or Hemoglobin of ≤ 7 g/dL, regardless of presence of clinical signs and/or symptoms). Patients randomized to anti-C5 treatment switched to LNP023 (iptacopan) on Day 169 and were treated until Day 336 (treatment extension period).

End point type	Primary
End point timeframe:	
Up to 48 weeks	
Notes:	

[4] - 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 planned for this primary outcome.

End point values	LNP023 200mg b.i.d.	Anti-C5 antibody		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	34		
Units: Participants				
Since Day 1 of LNP023 treatment	51	31		
Since Day 14 of LNP023 treatment	57	32		

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in FACIT-Fatigue questionnaire at Day 336

End point title	Change from baseline in FACIT-Fatigue questionnaire at Day 336

End point description:

The FACIT-Fatigue is a 13-item questionnaire with support for its validity and reliability in PNH that assesses patient self-reported fatigue and its impact on daily activities and function. All FACIT scales are scored so that a high score is better. As each of the 13 items of the FACIT-F Scale ranges from 0-4, the range of possible scores is 0-52, with 0 being the worst possible score and 52 the best.
Patients randomized to anti-C5 treatment switched to LNP023 (iptacopan) on Day 169 and were treated until Day 336 (treatment extension period).

End point type	Primary

End point timeframe:

Baseline, Day 336

End point values	LNP023 200mg b.i.d.	Anti-C5 antibody		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	26		
Units: score on a scale				
arithmetic mean (confidence interval 95%)	9.80 (8.04 to 11.56)	10.96 (8.58 to 13.34)		

Statistical analyses

Statistical analysis title	Analysis of FACIT Fatigue scores at day 336
Comparison groups	LNP023 200mg b.i.d. v Anti-C5 antibody
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Adjusted mean difference
Point estimate	-1.17

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.01
upper limit	1.68

Primary: Adjusted annualized clinical BTH rate after the start of LNP023 treatment

End point title	Adjusted annualized clinical BTH rate after the start of LNP023 treatment[5]

End point description:

This endpoint is considering clinical BTH events after the start of LNP023 treatment. Therefore, results are presented in a single arm on LNP023 since it includes all patients in the Combined Full analysis set. Adjusted annualized rate of clinical breakthrough hemolysis (BTH) events are from negative binomial model. A patient with multiple occurrences of an event under one treatment is counted only once for that treatment.The breakthrough is defined clinical if either there is a decrease in hemoglobin levels equal to or more than 2 g/dL (compared to the latest assessment, or within 15 days) or if patients present signs or symptoms of gross hemoglobinuria, painful crisis, dysphagia or any other significant clinical PNH-related signs & symptoms, in presence of laboratory evidence of intravascular hemolysis.

End point type	Primary

End point timeframe:

Up to 336 Days

Notes:

[5] - 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 planned for this primary outcome.

End point values	Combined full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	96			
Units: BTH events/year				
number (confidence interval 95%)	0.11 (0.05 to 0.23)			

Statistical analyses

No statistical analyses for this end point

Primary: Adjusted annualized Major Adverse Vascular Events rate after the start of LNP023 treatment

End point title	Adjusted annualized Major Adverse Vascular Events rate after the start of LNP023 treatment[6]

End point description:

This endpoint is considering clinical BTH events after the start of LNP023 treatment. Therefore, results are presented in a single arm on LNP023 since it includes all patients in the Combined Full analysis set. Adjusted annualized Major Adverse Vascular Events (MAVEs incl. thrombosis) rate. A MAVE is defined as: acute peripheral vascular occlusion, amputation (non-traumatic; nondiabetic), cerebral arterial occlusion/cerebrovascular accident, cerebral venous occlusion, dermal thrombosis, gangrene (non-traumatic; nondiabetic), hepatic/portal vein thrombosis (BuddChiari syndrome), mesenteric/visceral arterial, thrombosis or infarction, mesenteric/visceral vein thrombosis or infarction, myocardial infarction, pulmonary embolus, renal arterial thrombosis, renal vein thrombosis, thrombophlebitis / deep vein thrombosis, transient ischemic attack, unstable angina or other.
A patient with multiple occurrences of an event under one treatment is counted only once for that

treatment.

End point type	Primary
End point timeframe:	
Up to 336 Days	

Notes:

[6] - 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 planned for this primary outcome.

End point values	Combined full analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	96			
Units: MAVE events/year				
number (confidence interval 95%)	0.04 (0.01 to 0.13)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in absolute reticulocyte count in the randomized treatment period

End point title	Change from baseline in absolute reticulocyte count in the randomized treatment period
End point description:	
Change from baseline in absolute reticulocyte count as mean of visits between Day 126 and Day 168	
End point type	Secondary
End point timeframe:	
Baseline and mean of visits between Day 126 and 168	

End point values	LNP023 200mg b.i.d.	Anti-C5 antibody		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	35		
Units: x10^9 cells/L				
arithmetic mean (confidence interval 95%)	-115.81 (-126.40 to -105.23)	0.34 (-13.04 to 13.72)		

Statistical analyses

Statistical analysis title	Analysis of absolute reticulocyte counts
Comparison groups	LNP023 200mg b.i.d. v Anti-C5 antibody

Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	Mixed Model of Repeated Measures (MMRM)
Parameter estimate	Mean difference (net)
Point estimate	-116.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-132.04
upper limit	-100.26

Notes:

[7] - two sided unadjusted p-value

Secondary: Ratio to baseline in log-transformed LDH in the randomized treatment period

End point title	Ratio to baseline in log-transformed LDH in the randomized treatment period

End point description:

Average of the Lactate dehydrogenase (LDH) log transformed ratio to baseline in each treatment estimated between Day 126 and Day 168.The log transformation used refers to the natural log (base of e).

End point type	Secondary

End point timeframe:

Baseline and mean of visits between Day 126 and 168

End point values	LNP023 200mg b.i.d.	Anti-C5 antibody		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	35		
Units: ln(ratio)				
geometric mean (confidence interval 95%)	0.96 (0.90 to 1.03)	0.98 (0.89 to 1.07)		

Statistical analyses

Statistical analysis title	Analysis of LDH log-transformed ratio to baseline
Comparison groups	LNP023 200mg b.i.d. v Anti-C5 antibody
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8361 [8]
Method	Mixed Model of Repeated Measures (MMRM)
Parameter estimate	Geometric mean ratio
Point estimate	0.99

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.1

Notes:

[8] - two sided unadjusted p-value

Secondary: Adjusted annualized Major Adverse Vascular Events rate in the randomized treatment period

End point title	Adjusted annualized Major Adverse Vascular Events rate in the randomized treatment period

End point description:

Adjusted annualized Major Adverse Vascular Events (MAVEs incl. thrombosis) rate. A MAVE is defined as: acute peripheral vascular occlusion, amputation (non-traumatic; nondiabetic), cerebral arterial occlusion/cerebrovascular accident, cerebral venous occlusion, dermal thrombosis, gangrene (non-traumatic; nondiabetic), hepatic/portal vein thrombosis (BuddChiari syndrome), mesenteric/visceral arterial, thrombosis or infarction, mesenteric/visceral vein thrombosis or infarction, myocardial infarction, pulmonary embolus, renal arterial thrombosis, renal vein thrombosis, thrombophlebitis / deep vein thrombosis, transient ischemic attack, unstable angina or other.

 A patient with multiple occurrences of an event under one treatment is counted only once for that treatment.

End point type	Secondary

End point timeframe:

Between Day 1 and Day 168

End point values	LNP023 200mg b.i.d.	Anti-C5 antibody		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	35		
Units: MAVE events/year				
number (confidence interval 95%)	0.03 (0.00 to 0.25)	0.00 (0.00 to 0.00)		

Statistical analyses

Statistical analysis title	Rate of MAVEs
Comparison groups	LNP023 200mg b.i.d. v Anti-C5 antibody
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31731 [9]
Method	Poisson model
Parameter estimate	rate difference
Point estimate	0.03

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.1

Notes:

[9] - two sided unadjusted p-value

Secondary: Marginal proportion (expressed as percentages) of participants who remain free from transfusions

End point title	Marginal proportion (expressed as percentages) of participants who remain free from transfusions

End point description:

Marginal proportion (expressed as percentages) of participants who did not require transfusions between Day 14 and Day 168. Requiring red blood cell transfusions refers to any patient receiving transfusions or meeting protocol defined criteria (Hemoglobin level ≤ 9 g/dL with signs /and or symptoms of sufficient severity to warrant a transfusion or Hemoglobin of ≤ 7 g/dL, regardless of presence of clinical signs and/or symptoms). The term 'marginal proportion' can be interpreted as the population average probability of being a responder for each treatment group. These values include adjustment for baseline covariates and missing data has also been taken into account.

End point type	Secondary

End point timeframe:

Between Day 14 and Day 168

End point values	LNP023 200mg b.i.d.	Anti-C5 antibody		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	35		
Units: Percentage of participants				
number (confidence interval 95%)	94.8 (88.1 to 100.0)	25.9 (11.6 to 42.4)		

Statistical analyses

Statistical analysis title	Analysis of transfusion avoidance

Statistical analysis description:

logistic regression model

Comparison groups	LNP023 200mg b.i.d. v Anti-C5 antibody
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Diff. in marginal proportion
Point estimate	68.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	51.4
upper limit	83.9

Statistical analysis title	Analysis of transfusion avoidance
Comparison groups	LNP023 200mg b.i.d. v Anti-C5 antibody
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [10]
Method	Conditional logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	108.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.25
upper limit	681.24

Notes:

[10] - two sided unadjusted p-value

Secondary: Change from baseline in FACIT-Fatigue questionnaire in the Randomized Treatment Period

End point title	Change from baseline in FACIT-Fatigue questionnaire in the Randomized Treatment Period

End point description:

The FACIT-Fatigue is a 13-item questionnaire with support for its validity and reliability in PNH that assesses patient self-reported fatigue and its impact on daily activities and function. All FACIT scales are scored so that a high score is better. As each of the 13 items of the FACIT-F Scale ranges from 0-4, the range of possible scores is 0-52, with 0 being the worst possible score and 52 the best.

End point type	Secondary

End point timeframe:

Baseline, mean of visits between Day 126 and Day 168

End point values	LNP023 200mg b.i.d.	Anti-C5 antibody		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	33		
Units: score on a scale				
arithmetic mean (confidence interval 95%)	8.59 (6.72 to 10.47)	0.31 (-2.20 to 2.81)		

Statistical analyses

Statistical analysis title	Analysis of FACIT Fatigue scores
Comparison groups	LNP023 200mg b.i.d. v Anti-C5 antibody

Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [11]
Method	Mixed Model of Repeated Measures (MMRM)
Parameter estimate	Mean difference (net)
Point estimate	8.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.28
upper limit	11.29

Notes:

[11] - two sided unadjusted p-value

Secondary: Change from baseline in hemoglobin between Day 126 and 168

End point title	Change from baseline in hemoglobin between Day 126 and 168

End point description:

Change from baseline in hemoglobin levels as mean of visits between Day 126 and Day 168.
For this analysis, in order to factor out the effect of transfusions, if a patient had a transfusion during the randomized treatment period, then the hemoglobin values 30 days following the transfusion were excluded and hemoglobin data were imputed.

End point type	Secondary

End point timeframe:

Baseline and mean of visits between Day 126 and 168

End point values	LNP023 200mg b.i.d.	Anti-C5 antibody		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	35		
Units: g/dL				
arithmetic mean (confidence interval 95%)	3.60 (3.33 to 3.88)	-0.06 (-0.45 to 0.34)		

Statistical analyses

Statistical analysis title	Analysis of hemoglobin levels
Comparison groups	LNP023 200mg b.i.d. v Anti-C5 antibody
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Mixed Model of Repeated Measures (MMRM)
Parameter estimate	Adjusted mean diff.
Point estimate	3.66

Confidence interval	
level	95 %
sides	2-sided
lower limit	3.2
upper limit	4.12

Notes:

[12] - two sided unadjusted p-value

Secondary: Adjusted annualized clinical BTH rate in the randomized treatment period

End point title	Adjusted annualized clinical BTH rate in the randomized treatment period

End point description:

Adjusted annualized rate of clinical breakthrough hemolysis (BTH) events are from negative binomial model.
A patient with multiple occurrences of an event under one treatment is counted only once for that treatment.
The breakthrough is defined clinical if either there is a decrease in hemoglobin levels equal to or more than 2 g/dL (compared to the latest assessment, or within 15 days) or if patients present signs or symptoms of gross hemoglobinuria, painful crisis, dysphagia or any other significant clinical PNH-related signs & symptoms, in presence of laboratory evidence of intravascular hemolysis.

End point type	Secondary

End point timeframe:

Between Day 1 and Day 168

End point values	LNP023 200mg b.i.d.	Anti-C5 antibody		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	35		
Units: BTH events/year				
number (confidence interval 95%)	0.07 (0.02 to 0.31)	0.67 (0.26 to 1.72)		

Statistical analyses

Statistical analysis title	Adjusted annualized BTH rate
Comparison groups	LNP023 200mg b.i.d. v Anti-C5 antibody
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01183 [13]
Method	Negative binomial model
Parameter estimate	Rate ratio
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.61

Notes:

[13] - two sided unadjusted p-value

Statistical analysis title	Adjusted annualized BTH rate
Comparison groups	LNP023 200mg b.i.d. v Anti-C5 antibody
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Rate difference
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.24
upper limit	0.04

Other pre-specified: Change from baseline in absolute reticulocyte count at Day 336

End point title	Change from baseline in absolute reticulocyte count at Day 336

End point description:

Change from baseline in absolute reticulocyte count at visit Day 336.
Patients randomized to anti-C5 antibody were switched to LNP023 (iptacopan) on Day 169 and were treated until Day 336 (treatment extension period).

End point type	Other pre-specified

End point timeframe:

Baseline and Day 336

End point values	LNP023 200mg b.i.d.	Anti-C5 antibody		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	30		
Units: x10^9 cells/L				
arithmetic mean (confidence interval 95%)	-106.26 (-117.57 to -94.96)	-107.95 (-123.18 to -92.73)		

Statistical analyses

Statistical analysis title	Analysis of absolute reticulocyte count
Comparison groups	LNP023 200mg b.i.d. v Anti-C5 antibody

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Adjusted mean difference
Point estimate	1.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.86
upper limit	20.23

Other pre-specified: Ratio to baseline in log-transformed LDH at Visit Day 336

End point title	Ratio to baseline in log-transformed LDH at Visit Day 336

End point description:

Average of the Lactate dehydrogenase (LDH) log transformed ratio to baseline at visit Day 336.The log transformation used refers to the natural log (base of e).
Patients randomized to anti-C5 treatment switched to LNP023 (iptacopan) on Day 169 and were treated until Day 336 (treatment extension period).

End point type	Other pre-specified

End point timeframe:

Baseline and Day 336

End point values	LNP023 200mg b.i.d.	Anti-C5 antibody		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	33		
Units: ln(ratio)				
geometric mean (confidence interval 95%)	1.11 (1.02 to 1.22)	0.99 (0.88 to 1.11)		

Statistical analyses

Statistical analysis title	Analysis of LDH at visit Day 336
Comparison groups	LNP023 200mg b.i.d. v Anti-C5 antibody
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric mean ratio
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.3

Adverse events

Adverse events information

Timeframe for reporting adverse events:	
Adverse events of LNP023 group were reported from first dose of study treatment until the end of study treatment plus 30 days, up to a maximum duration of 48 weeks	
Adverse event reporting additional description:	
Adverse events of anti-C5 antibody were reported from the date of first administration of anti-C5 study treatment in the randomized treatment period to the date of the last actual administration of anti-C5 antibody in the randomized treatment period.	
Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	LNP023 200mg b.i.d.
Reporting group description:	
LNP023 200mg b.i.d. (Randomized treatment period)	
Reporting group title	Any LNP023 200mg b.i.d.
Reporting group description: -	
Reporting group title	LNP023 200mg b.i.d.
Reporting group description:	
LNP023 200mg b.i.d. (Randomized treatment period + extension treatment period)	
Reporting group title	Anti-C5 antibody
Reporting group description:	
Anti-C5 antibody (Randomized treatment period)	

Serious adverse events	LNP023 200mg b.i.d.	Any LNP023 200mg b.i.d.	LNP023 200mg b.i.d.
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 62 (9.68%)	13 / 96 (13.54%)	9 / 62 (14.52%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myelodysplastic syndrome			
subjects affected / exposed	1 / 62 (1.61%)	1 / 96 (1.04%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	1 / 62 (1.61%)	1 / 96 (1.04%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 62 (0.00%)	1 / 96 (1.04%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza A virus test positive			
subjects affected / exposed	0 / 62 (0.00%)	0 / 96 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Sinus node dysfunction			
subjects affected / exposed	1 / 62 (1.61%)	1 / 96 (1.04%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 62 (1.61%)	1 / 96 (1.04%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Extravascular haemolysis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 96 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breakthrough haemolysis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 96 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatolithiasis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 96 (1.04%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst			

subjects affected / exposed	0 / 62 (0.00%)	1 / 96 (1.04%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hepatobiliary disorders

Jaundice

subjects affected / exposed	0 / 62 (0.00%)	0 / 96 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Portal vein thrombosis

subjects affected / exposed	0 / 62 (0.00%)	1 / 96 (1.04%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders

Acute kidney injury

subjects affected / exposed	0 / 62 (0.00%)	0 / 96 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bilirubinuria

subjects affected / exposed	0 / 62 (0.00%)	0 / 96 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders

Rhabdomyolysis

subjects affected / exposed	1 / 62 (1.61%)	1 / 96 (1.04%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations

Arthritis bacterial

subjects affected / exposed	0 / 62 (0.00%)	0 / 96 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

COVID-19

subjects affected / exposed	1 / 62 (1.61%)	1 / 96 (1.04%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 62 (0.00%)	1 / 96 (1.04%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 62 (1.61%)	1 / 96 (1.04%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral discitis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 96 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 96 (1.04%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic infection			
subjects affected / exposed	0 / 62 (0.00%)	1 / 96 (1.04%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection pseudomonal			
subjects affected / exposed	1 / 62 (1.61%)	1 / 96 (1.04%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonal sepsis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 96 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Anti-C5 antibody		
Total subjects affected by serious			

adverse events			
subjects affected / exposed	5 / 35 (14.29%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myelodysplastic syndrome			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza A virus test positive			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Sinus node dysfunction			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Extravascular haemolysis			

subjects affected / exposed	1 / 35 (2.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Breakthrough haemolysis				
subjects affected / exposed	1 / 35 (2.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Pancreatolithiasis				
subjects affected / exposed	0 / 35 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Ovarian cyst				
subjects affected / exposed	0 / 35 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Jaundice				
subjects affected / exposed	1 / 35 (2.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Portal vein thrombosis				
subjects affected / exposed	0 / 35 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	1 / 35 (2.86%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bilirubinuria				

subjects affected / exposed	1 / 35 (2.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Musculoskeletal and connective tissue disorders

Rhabdomyolysis

subjects affected / exposed	0 / 35 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Infections and infestations

Arthritis bacterial

subjects affected / exposed	1 / 35 (2.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

COVID-19

subjects affected / exposed	2 / 35 (5.71%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

Septic shock

subjects affected / exposed	0 / 35 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Pyelonephritis

subjects affected / exposed	0 / 35 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Intervertebral discitis

subjects affected / exposed	1 / 35 (2.86%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Cellulitis

subjects affected / exposed	0 / 35 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Systemic infection			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection pseudomonal			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pseudomonal sepsis			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	LNP023 200mg b.i.d.	Any LNP023 200mg b.i.d.	LNP023 200mg b.i.d.
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 62 (54.84%)	62 / 96 (64.58%)	43 / 62 (69.35%)
Investigations			
Blood lactate dehydrogenase increased			
subjects affected / exposed	4 / 62 (6.45%)	6 / 96 (6.25%)	6 / 62 (9.68%)
occurrences (all)	4	6	6
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 62 (4.84%)	6 / 96 (6.25%)	4 / 62 (6.45%)
occurrences (all)	3	7	4
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 62 (17.74%)	14 / 96 (14.58%)	12 / 62 (19.35%)
occurrences (all)	18	24	22
Dizziness			
subjects affected / exposed	4 / 62 (6.45%)	4 / 96 (4.17%)	4 / 62 (6.45%)
occurrences (all)	5	5	5
Blood and lymphatic system disorders			

Thrombocytopenia			
subjects affected / exposed	3 / 62 (4.84%)	5 / 96 (5.21%)	3 / 62 (4.84%)
occurrences (all)	3	5	3
Breakthrough haemolysis			
subjects affected / exposed	2 / 62 (3.23%)	7 / 96 (7.29%)	6 / 62 (9.68%)
occurrences (all)	2	8	7
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 62 (3.23%)	5 / 96 (5.21%)	4 / 62 (6.45%)
occurrences (all)	3	7	5
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 62 (6.45%)	5 / 96 (5.21%)	5 / 62 (8.06%)
occurrences (all)	5	6	6
Diarrhoea			
subjects affected / exposed	9 / 62 (14.52%)	12 / 96 (12.50%)	10 / 62 (16.13%)
occurrences (all)	10	15	12
Nausea			
subjects affected / exposed	6 / 62 (9.68%)	11 / 96 (11.46%)	8 / 62 (12.90%)
occurrences (all)	8	14	10
Vomiting			
subjects affected / exposed	2 / 62 (3.23%)	5 / 96 (5.21%)	2 / 62 (3.23%)
occurrences (all)	2	6	2
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 62 (4.84%)	4 / 96 (4.17%)	4 / 62 (6.45%)
occurrences (all)	3	4	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 62 (8.06%)	7 / 96 (7.29%)	7 / 62 (11.29%)
occurrences (all)	6	9	9
Back pain			
subjects affected / exposed	3 / 62 (4.84%)	3 / 96 (3.13%)	3 / 62 (4.84%)
occurrences (all)	3	3	3
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	7 / 62 (11.29%)	12 / 96 (12.50%)	9 / 62 (14.52%)
occurrences (all)	7	12	9
Sinusitis			
subjects affected / exposed	2 / 62 (3.23%)	3 / 96 (3.13%)	3 / 62 (4.84%)
occurrences (all)	2	3	3
Upper respiratory tract infection			
subjects affected / exposed	2 / 62 (3.23%)	4 / 96 (4.17%)	3 / 62 (4.84%)
occurrences (all)	3	7	6
Urinary tract infection			
subjects affected / exposed	4 / 62 (6.45%)	7 / 96 (7.29%)	7 / 62 (11.29%)
occurrences (all)	4	7	7
COVID-19			
subjects affected / exposed	4 / 62 (6.45%)	25 / 96 (26.04%)	17 / 62 (27.42%)
occurrences (all)	4	27	18

Non-serious adverse events	Anti-C5 antibody		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 35 (60.00%)		
Investigations			
Blood lactate dehydrogenase increased			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	3		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Thrombocytopenia			

subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Breakthrough haemolysis			
subjects affected / exposed	6 / 35 (17.14%)		
occurrences (all)	10		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 35 (8.57%)		
occurrences (all)	4		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	2 / 35 (5.71%)		
occurrences (all)	2		
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	3 / 35 (8.57%)
occurrences (all)	3
Sinusitis	
subjects affected / exposed	3 / 35 (8.57%)
occurrences (all)	3
Upper respiratory tract infection	
subjects affected / exposed	3 / 35 (8.57%)
occurrences (all)	3
Urinary tract infection	
subjects affected / exposed	1 / 35 (2.86%)
occurrences (all)	1
COVID-19	
subjects affected / exposed	7 / 35 (20.00%)
occurrences (all)	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 March 2021	This amendment was implemented to add a sub-study for patient interviews to further explore the clinical meaningfulness of the effects with PROs (specifically the FACIT-Fatigue), to address contraception periods following anti-C5 antibody treatment discontinuation, to provide more clarity to certain inclusion/exclusion criteria, concomitant therapy, and prohibited medication, to ensure consistency throughout the protocol, as well as to clarify aspects related to the COVID-19 pandemic.
02 November 2021	This amendment was implemented to add a supplementary estimand considering the use of rescue therapy as treatment failure. Changes were also implemented to provide a more comprehensive evaluation of patients' hematology parameters by the central laboratory, by replacing the abbreviated hematology assessments with full hematology assessments. Clarifications were made in the statistical analysis section. In addition, simplification of the analyses of the PRO have been introduced. Other changes included new juvenile toxicity animal data, updated exclusion criterion on ravulizumab dose, further clarification on severe kidney disease (by adding eGFR < 30 mL/min/1.73 m2), and additional clarity of AE/SAE reporting post-treatment discontinuation, and new requirements regarding SAE reporting.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported