



## 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	v1
This version publication date	05 October 2023
First version publication date	05 October 2023

### Trial information

#### Trial identification

Sponsor protocol code	CLNP023C12302
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#### 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	Interim
Date of interim/final analysis	26 September 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 September 2022
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  $\geq 2$  g/dL (assessed between Day 126 and Day 168) in the absence of RBC transfusion between Day 14 and Day 168.
- Hb levels  $\geq 12$  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:

<b>Subjects enrolled per age group</b>	
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:

1 patient in the LNP023 group discontinued study treatment due to pregnancy, but continued study assessments until the end of Randomized Treatment Period (RTP).

### 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
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<b>Arm title</b>	LNP023 200mg b.i.d.
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Arm description:

iptacopan 200mg b.i.d. hard gelatin capsule

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.

<b>Arm title</b>	Anti-C5 antibody
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Arm description:

patients continued with the same stable regimen as that 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.

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 300 mg/30mL intravenous infusion

Investigational medicinal product name	Ecuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ecuzumab 300 mg/30mL concentrate solution for infusion

Number of subjects in period 1	LNP023 200mg b.i.d.	Anti-C5 antibody
Started	62	35
Completed	61	35
Not completed	1	0
Pregnancy	1	-

## 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
<b>Arm title</b>	LNP023 200mg b.i.d.

Arm description:

iptacopan 200mg b.i.d. hard gelatin capsule

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.

<b>Arm title</b>	Anti-C5 antibody
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Arm description:

patients continued with the same stable regimen as that 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.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 2<sup>[1]</sup></b>	<b>LNP023 200mg b.i.d.</b>	<b>Anti-C5 antibody</b>
Started	61	33
Completed	32	19
Not completed	29	14
Pregnancy	1	-
Ongoing at time of data cut-off date 2022-09-26	28	14

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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 96 patients completing the Randomized Treatment Period, 94 entered the treatment extension period. Two patients, initially randomized to anti-C5, did not enter the extension period.

## Baseline characteristics

### Reporting groups

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

iptacopan 200mg b.i.d. hard gelatin capsule

Reporting group title	Anti-C5 antibody
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Reporting group description:

patients continued with the same stable regimen as that 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.

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

## 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	
Reporting group title	Anti-C5 antibody
Reporting group description: patients continued with the same stable regimen as that 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.	
Reporting group title	LNP023 200mg b.i.d.
Reporting group description: iptacopan 200mg b.i.d. hard gelatin capsule	
Reporting group title	Anti-C5 antibody
Reporting group description: patients continued with the same stable regimen as that 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.	

### Primary: Marginal proportion of participants with sustained increase in hemoglobin levels from baseline of $\geq 2$ g/dL in the absence of red blood cell transfusions

End point title	Marginal proportion of participants with sustained increase in hemoglobin levels from baseline of $\geq 2$ g/dL in the absence of red blood cell transfusions
End point description: 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: marginal proportion of participants				
number (confidence interval 95%)	82.3 (73.4 to 90.2)	2.0 (1.1 to 4.1)		



## Statistical analyses

<b>Statistical analysis title</b>	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 <sup>[1]</sup>
P-value	< 0.0001 <sup>[2]</sup>
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	338.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	25.12
upper limit	4567.99

Notes:

[1] - Logistic regression model using Firth

[2] - two sided unadjusted p-value

## Primary: Marginal proportion of participants with sustained hemoglobin levels of $\geq 12$ g/dL in the absence of red blood cell transfusions

End point title	Marginal proportion of participants with sustained hemoglobin levels of $\geq 12$ g/dL in the absence of red blood cell transfusions
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End point description:

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
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End point timeframe:

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

<b>End point values</b>	LNP023 200mg b.i.d.	Anti-C5 antibody		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	35		
Units: marginal proportion of participants				
number (confidence interval 95%)	68.8 (58.3 to 78.9)	1.8 (0.9 to 4.0)		

## Statistical analyses

<b>Statistical analysis title</b>	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 <sup>[3]</sup>
P-value	< 0.0001 <sup>[4]</sup>
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	496.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	24.44
upper limit	10096.85

Notes:

[3] - Logistic regression model using Firth

[4] - two sided unadjusted p-value

## Secondary: Marginal proportion of participants who remain free from transfusions

End point title	Marginal proportion of participants who remain free from transfusions
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End point description:

Marginal proportion 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
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End point timeframe:

Between Day 14 and Day 168

<b>End point values</b>	LNP023 200mg b.i.d.	Anti-C5 antibody		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	35		
Units: Marginal proportion of participants				
number (confidence interval 95%)	96.4 (90.7 to 100.0)	26.1 (12.4 to 42.7)		

## Statistical analyses

<b>Statistical analysis title</b>	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 <sup>[5]</sup>
Method	Conditional logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	133.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	19.78
upper limit	901.44

Notes:

[5] - two sided unadjusted p-value

## Secondary: Change from baseline in hemoglobin in the randomized treatment period

End point title	Change from baseline in hemoglobin in the randomized treatment period
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End point description:

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
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End point timeframe:

Baseline and mean of visits between Day 126 and 168

<b>End point values</b>	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%)	3.59 (3.32 to 3.86)	-0.04 (-0.42 to 0.35)		

## Statistical analyses

<b>Statistical analysis title</b>	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 <sup>[6]</sup>
Method	Mixed Model of Repeated Measures (MMRM)
Parameter estimate	Adjusted mean diff.
Point estimate	3.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.18
upper limit	4.08

Notes:

[6] - 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
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End point description:

Change from baseline in FACIT-Fatigue scores as mean of visits between Day 126 and Day 168. 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
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End point timeframe:

Baseline and mean of visits between Day 126 and Day 168

<b>End point values</b>	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

<b>Statistical analysis title</b>	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 <sup>[7]</sup>
P-value	< 0.0001
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:

[7] - two sided unadjusted p-value

### 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	

<b>End point values</b>	LNP023 200mg b.i.d.	Anti-C5 antibody		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	35		
Units: * 10 <sup>9</sup> /L				
arithmetic mean (confidence interval 95%)	-115.89 (-126.49 to -105.30)	0.37 (-13.03 to 13.77)		

### Statistical analyses

<b>Statistical analysis title</b>	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 <sup>[8]</sup>
Method	Mixed Model of Repeated Measures (MMRM)
Parameter estimate	Mean difference (net)
Point estimate	-116.26

Confidence interval	
level	95 %
sides	2-sided
lower limit	-132.17
upper limit	-100.36

Notes:

[8] - two sided unadjusted p-value

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

End point title	Adjusted annualized BTH rate in the randomized treatment period
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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
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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: Adjusted annualized BTH rate				
number (confidence interval 95%)				
Number of patients with at least 1 event(n:2; n:6)	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 <sup>[9]</sup>
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:

[9] - 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
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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
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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: LDH log-transformed ratio to baseline				
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	= 0.8345 <sup>[10]</sup>
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:

[10] - 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
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**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 (Budd-Chiari 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.

End point type	Secondary
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**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: Adjusted annualized MAVE rate				
number (confidence interval 95%)				
Number of patients with at least 1 event(n:1; n:0)	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	other
P-value	= 0.31731 <sup>[11]</sup>
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:**

[11] - two sided unadjusted p-value



## 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 the cut-off date (26-Sep-2022), up to a maximum duration of 48 weeks.

Adverse event reporting additional description:

Safety analyses summarize on-treatment (OT) events. The OT period of LNP023 lasts from the date of first admin. of study treatment to 7 days after the date of the last admin. of LNP023. The OT period of anti-C5 antibody lasts from the date of first admin. of anti-C5 treatment in the RTP to the date of the last admin. of anti-C5 antibody in the RTP.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.0
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### Reporting groups

Reporting group title	LNP023 200mg b.i.d. (Randomized treatment period)
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Reporting group description:

LNP023 200mg b.i.d. (Randomized treatment period)

Reporting group title	Any LNP023 200mg b.i.d.
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Reporting group description:

Any LNP023 200mg b.i.d.

Reporting group title	LNP023 200mg b.i.d. (Randomized + ext treatment period)
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Reporting group description:

LNP023 200mg b.i.d. (Randomized treatment period + extension treatment period)

Reporting group title	Anti-C5 antibody (Randomized treatment period)
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Reporting group description:

Anti-C5 antibody (Randomized treatment period)

Serious adverse events	LNP023 200mg b.i.d. (Randomized treatment period)	Any LNP023 200mg b.i.d.	LNP023 200mg b.i.d. (Randomized + ext treatment period)
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 62 (9.68%)	12 / 95 (12.63%)	9 / 62 (14.52%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 62 (1.61%)	1 / 95 (1.05%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
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 / 95 (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
Platelet count decreased			
subjects affected / exposed	0 / 62 (0.00%)	1 / 95 (1.05%)	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
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 62 (1.61%)	1 / 95 (1.05%)	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
Myelodysplastic syndrome			
subjects affected / exposed	1 / 62 (1.61%)	1 / 95 (1.05%)	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
Cardiac disorders			
Sinus node dysfunction			
subjects affected / exposed	1 / 62 (1.61%)	1 / 95 (1.05%)	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 / 95 (1.05%)	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			
Breakthrough haemolysis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 95 (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
Extravascular haemolysis			

subjects affected / exposed	0 / 62 (0.00%)	0 / 95 (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 / 95 (1.05%)	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 / 95 (1.05%)	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 / 95 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 62 (0.00%)	0 / 95 (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 / 95 (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
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 62 (1.61%)	1 / 95 (1.05%)	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
Cellulitis			

subjects affected / exposed	0 / 62 (0.00%)	1 / 95 (1.05%)	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
Intervertebral discitis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 95 (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
Pyelonephritis			
subjects affected / exposed	1 / 62 (1.61%)	1 / 95 (1.05%)	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
Sepsis			
subjects affected / exposed	0 / 62 (0.00%)	0 / 95 (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
Arthritis bacterial			
subjects affected / exposed	0 / 62 (0.00%)	0 / 95 (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
Septic shock			
subjects affected / exposed	0 / 62 (0.00%)	1 / 95 (1.05%)	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 / 95 (1.05%)	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			
subjects affected / exposed	1 / 62 (1.61%)	1 / 95 (1.05%)	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

<b>Serious adverse events</b>	Anti-C5 antibody (Randomized treatment period)		
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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		
Investigations			
Blood creatine phosphokinase increased			
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		
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		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
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		
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		
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			
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		
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		
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		
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		
Infections and infestations			
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		
Cellulitis			
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		
Pyelonephritis			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
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		
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		
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			
subjects affected / exposed	0 / 35 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	LNP023 200mg b.i.d. (Randomized treatment period)	Any LNP023 200mg b.i.d.	LNP023 200mg b.i.d. (Randomized + ext treatment period)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 62 (54.84%)	56 / 95 (58.95%)	40 / 62 (64.52%)
Investigations			
Blood lactate dehydrogenase increased			
subjects affected / exposed	4 / 62 (6.45%)	5 / 95 (5.26%)	5 / 62 (8.06%)
occurrences (all)	4	5	5
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 62 (4.84%)	5 / 95 (5.26%)	3 / 62 (4.84%)
occurrences (all)	3	5	3
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 62 (16.13%)	12 / 95 (12.63%)	10 / 62 (16.13%)
occurrences (all)	17	22	20
Dizziness			
subjects affected / exposed	4 / 62 (6.45%)	4 / 95 (4.21%)	4 / 62 (6.45%)
occurrences (all)	5	5	5
Blood and lymphatic system disorders			
Breakthrough haemolysis			
subjects affected / exposed	2 / 62 (3.23%)	5 / 95 (5.26%)	4 / 62 (6.45%)
occurrences (all)	2	6	5
Thrombocytopenia			



subjects affected / exposed occurrences (all)	3 / 62 (4.84%) 3	5 / 95 (5.26%) 5	3 / 62 (4.84%) 3
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	2 / 62 (3.23%) 3	2 / 95 (2.11%) 3	2 / 62 (3.23%) 3
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)  Diarrhoea subjects affected / exposed occurrences (all)  Abdominal pain subjects affected / exposed occurrences (all)	6 / 62 (9.68%) 8  9 / 62 (14.52%) 10  4 / 62 (6.45%) 5	9 / 95 (9.47%) 11  11 / 95 (11.58%) 14  5 / 95 (5.26%) 6	7 / 62 (11.29%) 9  9 / 62 (14.52%) 11  5 / 62 (8.06%) 6
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	3 / 62 (4.84%) 3	4 / 95 (4.21%) 4	4 / 62 (6.45%) 4
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)  Arthralgia subjects affected / exposed occurrences (all)	3 / 62 (4.84%) 3  5 / 62 (8.06%) 6	3 / 95 (3.16%) 3  7 / 95 (7.37%) 9	3 / 62 (4.84%) 3  7 / 62 (11.29%) 9
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)  Sinusitis subjects affected / exposed occurrences (all)  Nasopharyngitis	2 / 62 (3.23%) 3  2 / 62 (3.23%) 2	2 / 95 (2.11%) 4  3 / 95 (3.16%) 3	2 / 62 (3.23%) 4  3 / 62 (4.84%) 3

subjects affected / exposed occurrences (all)	7 / 62 (11.29%) 7	12 / 95 (12.63%) 12	9 / 62 (14.52%) 9
COVID-19 subjects affected / exposed occurrences (all)	4 / 62 (6.45%) 4	21 / 95 (22.11%) 23	14 / 62 (22.58%) 15
Urinary tract infection subjects affected / exposed occurrences (all)	4 / 62 (6.45%) 4	5 / 95 (5.26%) 5	5 / 62 (8.06%) 5

<b>Non-serious adverse events</b>	Anti-C5 antibody (Randomized treatment period)		
Total subjects affected by non-serious adverse events subjects affected / exposed	21 / 35 (60.00%)		
Investigations Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
Nervous system disorders Headache subjects affected / exposed occurrences (all)  Dizziness subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1  0 / 35 (0.00%) 0		
Blood and lymphatic system disorders Breakthrough haemolysis subjects affected / exposed occurrences (all)  Thrombocytopenia subjects affected / exposed occurrences (all)	6 / 35 (17.14%) 10  0 / 35 (0.00%) 0		
General disorders and administration site conditions			

Pyrexia subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 4		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)  Diarrhoea subjects affected / exposed occurrences (all)  Abdominal pain subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1  2 / 35 (5.71%) 2  1 / 35 (2.86%) 1		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)  Arthralgia subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2  1 / 35 (2.86%) 1		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)  Sinusitis subjects affected / exposed occurrences (all)  Nasopharyngitis subjects affected / exposed occurrences (all)  COVID-19	3 / 35 (8.57%) 3  3 / 35 (8.57%) 3  2 / 35 (5.71%) 2		

subjects affected / exposed	7 / 35 (20.00%)		
occurrences (all)	7		
Urinary tract infection			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		

## 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	<p>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.</p> <p>Other changes included new juvenile toxicity animal data, updated exclusion criterion on ravulizumab dose, further clarification on severe kidney disease (by adding eGFR &lt; 30 mL/min/1.73 m<sup>2</sup>), and additional clarity of AE/SAE reporting post-treatment discontinuation, and new requirements regarding SAE reporting.</p>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported