



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 |
|-----------------------|---------------|

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 ≥ 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:

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 |
|------------------------------|-----|

| | |
|------------------|---------------------|
| Arm title | 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.

| | |
|------------------|------------------|
| Arm title | Anti-C5 antibody |
|------------------|------------------|

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 | 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/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 |
| Arm title | 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.

| | |
|------------------|------------------|
| Arm title | Anti-C5 antibody |
|------------------|------------------|

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 | |

| Number of subjects in period 2 ^[1] | LNP023 200mg b.i.d. | Anti-C5 antibody |
|--|------------------------|------------------|
| | | |
| 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 |

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. |
|-----------------------|---------------------|

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 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 ≥ 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 ≥ 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

| | |
|---|--|
| 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 ^[1] |
| P-value | < 0.0001 ^[2] |
| 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 ≥ 12 g/dL in the absence of red blood cell transfusions

| | |
|-----------------|--|
| End point title | Marginal proportion of participants with sustained hemoglobin levels of ≥ 12 g/dL in the absence of red blood cell transfusions |
|-----------------|--|

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 |
|----------------|---------|

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: marginal proportion of participants | | | | |
| number (confidence interval 95%) | 68.8 (58.3 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 ^[3] |
| P-value | < 0.0001 ^[4] |
| 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 |
|-----------------|---|

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 |
|----------------|-----------|

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: Marginal proportion of participants | | | | |
| number (confidence interval 95%) | 96.4 (90.7 to 100.0) | 26.1 (12.4 to 42.7) | | |

Statistical analyses

| | |
|---|--|
| 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 ^[5] |
| 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 |
|-----------------|---|

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 |
|----------------|-----------|

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%) | 3.59 (3.32 to 3.86) | -0.04 (-0.42 to 0.35) | | |

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 ^[6] |
| 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 |
|-----------------|--|

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 |
|----------------|-----------|

End point timeframe:

Baseline and 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 ^[7] |
| 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 | |

| | | | | |
|---|------------------------------|------------------------|--|--|
| 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: * 10 ⁹ /L | | | | |
| arithmetic mean (confidence interval 95%) | -115.89 (-126.49 to -105.30) | 0.37 (-13.03 to 13.77) | | |

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 ^[8] |
| 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: 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: 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 ^[9] |
| 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:

[9] - 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 |
|-----------------|---|

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: 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 ^[10] |
| 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:

[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 |
|-----------------|---|

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 |
| 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 ^[11] |
| 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 |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 25.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | LNP023 200mg b.i.d. (Randomized treatment period) |
|-----------------------|---|

Reporting group description:

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

| | |
|-----------------------|-------------------------|
| Reporting group title | Any LNP023 200mg b.i.d. |
|-----------------------|-------------------------|

Reporting group description:

Any LNP023 200mg b.i.d.

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

Reporting group description:

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

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

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 |

| | | | |
|-------------------------------|--|--|--|
| Serious adverse events | Anti-C5 antibody (Randomized treatment period) | | |
|-------------------------------|--|--|--|

| | | | |
|---|-----------------|--|--|
| 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 %

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

| | | | |
|--|--|--|--|
| Non-serious adverse events | 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 | 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 | | | |
| Breakthrough haemolysis | | | |
| subjects affected / exposed | 6 / 35 (17.14%) | | |
| occurrences (all) | 10 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | | |
| occurrences (all) | 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 < 30 mL/min/1.73 m²), and additional clarity of AE/SAE reporting post-treatment discontinuation, and new requirements regarding SAE reporting.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported