# Sponsor

Novartis Pharmaceuticals

# Generic Drug Name

Iptacopan

# Trial Indication(s)

Paroxysmal nocturnal hemoglobinuria (PNH)

# Protocol Number

CLNP023C12302

# Protocol Title

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.

# Clinical Trial Phase

Phase 3

# Phase of Drug Development

Phase III

# Study Start/End Dates

Study Start Date: January 25, 2021 (Actual)

Primary Completion Date: September 26, 2022 (Actual)

Study Completion Date: March 06, 2023 (Actual)

# Reason for Termination

# Study Design/Methodology

This study was a multi-center, randomized, open-label, active comparator-controlled, parallel group study, comprising three periods:

• A screening period lasting up to 8 weeks (unless there was a need to extend it for vaccinations required for inclusion, vaccinations were started as early as possible to avoid extension of the screening period)

• A 24-week randomized, open-label, active controlled, treatment period for the primary efficacy and safety analyses

• A 24-week open-label, iptacopan treatment extension period

Eligible patients were randomized (8:5) to receive either iptacopan monotherapy at a dose of 200 mg orally b.i.d. or i.v. anti-C5 antibody treatment (with the same regimen during the randomized treatment period as they were prior to randomization).

The study enrolled PNH patients with residual anemia, defined as hemoglobin < 10 g/dL, despite a stable regimen of anti-C5 antibody treatment (eculizumab or ravulizumab) in the last 6 months before randomization.

The database of the study was locked for the randomized treatment period after all patients had completed the Day 168 visit in the study or EOS (End of Study) for patients who had discontinued the study prior to the treatment extension period. The final database lock took place after the last patient had completed the last visit (Day 336 or EOS) in the treatment extension period.

# Centers

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

# Objectives:

**Objectives for the randomized treatment period:**

Primary Objective:

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.

Secondary Objectives:

* To demonstrate superiority of iptacopan, compared to anti-C5 antibody treatment in transfusion avoidance as the proportion of patients who remain free from transfusions.
* To demonstrate superiority of iptacopan, compared to anti-C5 antibody treatment, in average change in hemoglobin.
* To demonstrate superiority of iptacopan, compared to anti-C5 antibody treatment, in improving fatigue, using the FACITFatigue questionnaire.
* To demonstrate superiority of iptacopan, compared to anti-C5 antibody treatment, in average change in reticulocyte counts.
* To demonstrate superiority of iptacopan, compared to anti-C5 antibody treatment, in average percent change in LDH.
* To demonstrate superiority of iptacopan, compared to anti-C5 antibody treatment, in the rate of breakthrough hemolysis (BTH).
* To assess the rates of Major Adverse Vascular Events (MAVEs incl. thrombosis) of iptacopan, compared to anti-C5 antibody treatment.
* To assess safety and tolerability of iptacopan compared to anti-C5 antibody treatment.

**Objectives for the treatment extension period:**

The primary objective was to assess long term safety, tolerability and efficacy of LNP023.

# Test Product (s), Dose(s), and Mode(s) of Administration

* Iptacopan monotherapy at a dose of 200 mg orally b.i.d.
* Anti-C5 antibody treatment:
	+ Eculizumab concentrate solution for infusion of 300 mg/30mL
	+ Ravulizumab concentrate solution for infusion of 300 mg/30mL, 300 mg/3 mL and 1100 mg/11 mL.

# Statistical Methods

**Analysis of Randomized treatment period:**

Efficacy endpoints

The analysis of efficacy variables was based on the full analysis set (FAS) that included all patients randomized into the study. The overall study Type I error was one-sided 0.025. The multiplicity adjustment was applied for the test of two primary endpoints as well as to the secondary endpoints for controlling the study wise Type I error.

Superiority of iptacopan in achieving a larger proportion of patients who reached a sustained hemoglobin response compared to anti-C5 antibody treatment was tested for each of the two primary endpoints, separately.

Analysis of primary endpoint:For each of the two primary endpoints, the test of hypothesis was initially implemented by fitting a conditional logistic regression model, which conditioned on stratum within which patients were randomized, and included as covariates both sex, age (indicator of age ≥ 45 years), and an indicator variable of baseline hemoglobin above 9 g/dL. However, these analyses models did not converge due to zero responders in the anti-C5 arm. Hence, the test of the hypotheses associated to the two primary endpoints were carried out by fitting a logistic regression model, based on Firth’s penalized maximum likelihood method (Heinze and Schemper 2002, Firth 1993).

Analysis of secondary endpoints:

Transfusion avoidance was evaluated by comparing the proportion of patients not receiving nor meeting the criteria for administration of RBC transfusion between Day 14 and Day 168. The comparison of treatments was carried out by means of the odds ratio derived using conditional logistic regression with standardized marginal proportions derived using logistic regression.

Comparison of mean change from baseline in hemoglobin levels: data collected within 30 days after transfusion were discarded and imputed under MAR (missing at random) assumptions using the hemoglobin data not impacted by transfusion.

The model for the comparison between treatments was a repeated measures model with an unstructured covariance structure, with stratification factors, age (binary indicator), sex and including main effect of treatment, visit and baseline, and the interactions between visits and treatment and visits and baseline levels. The treatment contrasts were computed as the comparison of treatments corresponding to the average measured in the last 6 weeks of randomized treatment (that is the visits occurring between Day 126 and Day 168).

The endpoint consisted of changes from baseline in scores of fatigue using the FACIT-Fatigue questionnaire. The comparison between treatments was an average of treatment estimates derived for visits occurring between Day 126 and Day 168 as obtained from a repeated measures model. The model included the main effects of stratification factors, treatment baseline covariates and interaction terms.

The comparison of the mean change from baseline in reticulocyte counts was derived from a longitudinal repeated measures model including data collected throughout the study. The comparison between treatments used the average of model derived estimates for each treatment obtained at visits occurring between Day 126 and Day 168 as obtained from a repeated measures model. The model included stratification factors, treatment, baseline and interaction terms.

The treatment effect on percent change from baseline in LDH was assessed using a longitudinal repeated measures model of log transformed ratio to baseline based on all observations collected during the randomized period. The model is same as the model described for all continuous endpoints. Treatment comparisons were derived based on the average of the log transformed ratio in each treatment estimated between Day 126 and Day 168.

The comparison of rates of breakthrough hemolysis was carried out using a negative binomial model. The model planned to include the following covariates: treatment, randomization strata, sex, age (indicator of age ≥ 45 years), indicator variable of baseline hemoglobin ≥ 9 g/dL. Following the treatment policy strategy for handling treatment discontinuations, the offset variable was defined as the time from Day 1 till minimum (end of study, end of randomized treatment period).

For the analysis a negative binomial model with treatment as a factor was implemented.

The comparison of rates of Major Adverse Vascular Events (MAVE) was planned to be carried out using a negative binomial model using treatment as a factor. For the analysis on the secondary endpoint the Poisson model with treatment as a factor was implemented. Due to presence of only event the rate ratio could not be computed, hence rate difference and corresponding p-value were presented.

**Analysis of treatment extension period**:

For all efficacy analyses based on laboratory data (e.g. hemoglobin, absolute reticulocyte counts, LDH), the information obtained from the central lab was used. Analyses were conducted on the combined FAS (all patients randomized to LNP023 200 mg b.i.d and all patientsrandomized to anti-C5 treatment and who switched to LNP023 in the treatment extension period) when the intention is to analyze efficacy based on iptacopan use. Analyses were done on the FAS (all patients to whom study treatment has been assigned by randomization) when the intention is to analyze efficacy data based on the entire 48-week study duration (Day 1-336) and by the randomized treatment arms (iptacopan-iptacopan; anti-C5 antibody- iptacopan). All summaries were based on observed data.

# Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

• Male and female participants ≥ 18 years of age with a diagnosis of PNH confirmed by high-sensitivity flow cytometry with clone size ≥ 10%

• Stable regimen of anti-C5 antibody treatment (either eculizumab or ravulizumab) for at least 6 months prior to randomization

• Mean hemoglobin level <10 g/dL

• Vaccination against Neisseria meningitidis infection is required prior to the start of treatment.

• If not received previously, vaccination against Streptococcus pneumoniae and Haemophilus influenzae infections should be given

Exclusion Criteria:

• Participants on a stable eculizumab dose but with a dosing interval of 11 days or less or patients

on stable ravulizumab dose but with a dosing interval of less than 8 weeks.

• Known or suspected hereditary complement deficiency at screening

• History of hematopoietic stem cell transplantation

• Patients with laboratory evidence of bone marrow failure (reticulocytes <100x10E9/L; platelets <30x10E9/L; neutrophils <500x10E6/L).

• Active systemic bacterial, viral (incl. COVID-19), or fungal infection within 14 days prior to study drug administration

• A history of recurrent invasive infections caused by encapsulated organisms, e.g. meningococcus or pneumococcus.

• Major concurrent comorbidities including but not limited to severe kidney disease (e.g., eGFR < 30 mL/min/1.73 m2, dialysis), advanced cardiac disease (e.g., NYHA class IV), severe pulmonary disease (e.g., severe pulmonary hypertension (WHO class IV)), or hepatic disease (e.g., active hepatitis) that in the opinion of the investigator precludes participant's participation in the study.

# Participant Flow Table

|  |
| --- |
| **Randomized treatment period** |
|  | **LNP023 200mg b.i.d.** | **Anti-C5 antibody** | **Total**  |
| **Arm/Group Description**  | **Iptacopan 200mg b.i.d. hard gelatin capsule.
After 24 weeks of LNP023 200mg b.i.d. treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive an additional 24 weeks of LNP023 200mg b.i.d.** | **In the Randomized Treatment Period patients randomized to receive Anti-C5 antibody continued with the same stable regimen of Anti-C5 antibody therapy as they had received prior to randomization. For eculizumab (administered as intravenous infusion every 2 weeks), the maintenance dose was a fixed dose, whereas for ravulizumab (administered as intravenous infusion every 8 weeks), the maintenance dose was based on body weight. After 24 weeks of Anti-C5 antibody treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive 24 weeks of LNP023 200mg b.i.d.** |  |
| **Started**  | **62** | **35** | **97** |
| **Completed**  | **62** | **35** | **97** |
| **Not Completed**  | **0** | **0** | **0** |

|  |
| --- |
| **Extension treatment period** |
|  | **LNP023 200mg b.i.d.** | **Anti-C5 antibody** | **Total**  |
| **Arm/Group Description**  | **Iptacopan 200mg b.i.d. hard gelatin capsule.
After 24 weeks of LNP023 200mg b.i.d. treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive an additional 24 weeks of LNP023 200mg b.i.d.** | **In the Randomized Treatment Period patients randomized to receive Anti-C5 antibody continued with the same stable regimen of Anti-C5 antibody therapy as they had received prior to randomization. For eculizumab (administered as intravenous infusion every 2 weeks), the maintenance dose was a fixed dose, whereas for ravulizumab (administered as intravenous infusion every 8 weeks), the maintenance dose was based on body weight. After 24 weeks of Anti-C5 antibody treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive 24 weeks of LNP023 200mg b.i.d.** |  |
| **Started**  | **61** | **34** | **95** |
| **Full Analysis Set** | **62** | **35** | **97** |
| **Combined full analysis set** | **62** | **34** | **96** |
| **Completed**  | **61** | **34** | **95** |
| **Not Completed**  | **0** | **0** | **0** |

# Baseline Characteristics

|  |  |  |  |
| --- | --- | --- | --- |
|  | **LNP023 200mg b.i.d.** | **Anti-C5 antibody** |  **Total**  |
| **Arm/Group Description**  | **Iptacopan 200mg b.i.d. hard gelatin capsule.
After 24 weeks of LNP023 200mg b.i.d. treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive an additional 24 weeks of LNP023 200mg b.i.d.** | **In the Randomized Treatment Period patients randomized to receive Anti-C5 antibody continued with the same stable regimen of Anti-C5 antibody therapy as they had received prior to randomization. For eculizumab (administered as intravenous infusion every 2 weeks), the maintenance dose was a fixed dose, whereas for ravulizumab (administered as intravenous infusion every 8 weeks), the maintenance dose was based on body weight. After 24 weeks of Anti-C5 antibody treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive 24 weeks of LNP023 200mg b.i.d.** |  |
|  **Number of Participants [units: participants]**  | **62** | **35** | **97** |
|  **Baseline Analysis Population Description**  |  |
| **Age Continuous(units: years)
 Analysis Population Type: ParticipantsMean ± Standard Deviation** |
|  | **51.7±16.94** | **49.8±16.69** | **51.0±16.79** |
| **Sex: Female, Male(units: participants)
 Analysis Population Type: ParticipantsCount of Participants (Not Applicable)** |
| **Female** | **43** | **24** | **67** |
| **Male** | **19** | **11** | **30** |
| **Race/Ethnicity, Customized(units: participants)
 Analysis Population Type: ParticipantsCount of Participants (Not Applicable)** |
| **White** | **48** | **26** | **74** |
| **Black or African American** | **2** | **2** | **4** |
| **Asian** | **12** | **7** | **19** |

# Primary Outcome Result(s)

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

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

|  |  |  |
| --- | --- | --- |
|  | **LNP023 200mg b.i.d.** | **Anti-C5 antibody** |
| **Arm/Group Description**  | **Iptacopan 200mg b.i.d. hard gelatin capsule.
After 24 weeks of LNP023 200mg b.i.d. treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive an additional 24 weeks of LNP023 200mg b.i.d.** | **In the Randomized Treatment Period patients randomized to receive Anti-C5 antibody continued with the same stable regimen of Anti-C5 antibody therapy as they had received prior to randomization. For eculizumab (administered as intravenous infusion every 2 weeks), the maintenance dose was a fixed dose, whereas for ravulizumab (administered as intravenous infusion every 8 weeks), the maintenance dose was based on body weight. After 24 weeks of Anti-C5 antibody treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive 24 weeks of LNP023 200mg b.i.d.** |
|  **Number of Participants Analyzed [units: participants]** | **62** | **35** |
| **Marginal proportion (expressed as percentages) of participants with sustained increase in hemoglobin levels from baseline of ≥ 2 g/dL in the absence of red blood cell transfusions(units: Percentage of responders)**  | **Number (95% Confidence Interval)** | **Number (95% Confidence Interval)** |
|  | **82.3(73.4 to 90.2)**  | **2.0(1.1 to 4.0)**  |

## Statistical Analysis

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| --- | --- | --- |
| **Groups** | **LNP023 200mg b.i.d.,Anti-C5 antibody** |  |
|  **Type of Statistical Test**  | **Superiority** |  |
|  **P Value**  | **<0.0001** | **two sided unadjusted p-value** |
|  **Method**  | **Regression, Logistic** | **Logistic regression model using Firth** |
| **Odds Ratio (OR)** | **338.25** |  |
| **95% Confidence Interval2-Sided** | **25.07 to 4564.14** |  |

## Statistical Analysis

|  |  |  |
| --- | --- | --- |
| **Groups** | **LNP023 200mg b.i.d.,Anti-C5 antibody** |  |
|  **Type of Statistical Test**  | **Superiority** |  |
| **OtherDifference in marginal proportion** | **80.2** |  |
| **95% Confidence Interval2-Sided** | **71.2 to 87.6** |  |

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

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

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| --- | --- | --- |
|  | **LNP023 200mg b.i.d.** | **Anti-C5 antibody** |
| **Arm/Group Description**  | **Iptacopan 200mg b.i.d. hard gelatin capsule.
After 24 weeks of LNP023 200mg b.i.d. treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive an additional 24 weeks of LNP023 200mg b.i.d.** | **In the Randomized Treatment Period patients randomized to receive Anti-C5 antibody continued with the same stable regimen of Anti-C5 antibody therapy as they had received prior to randomization. For eculizumab (administered as intravenous infusion every 2 weeks), the maintenance dose was a fixed dose, whereas for ravulizumab (administered as intravenous infusion every 8 weeks), the maintenance dose was based on body weight. After 24 weeks of Anti-C5 antibody treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive 24 weeks of LNP023 200mg b.i.d.** |
|  **Number of Participants Analyzed [units: participants]** | **62** | **35** |
| **Marginal proportion (expressed as percentages) of participants with sustained hemoglobin levels of ≥ 12 g/dL in the absence of red blood cell transfusions(units: Percentage of responders)**  | **Number (95% Confidence Interval)** | **Number (95% Confidence Interval)** |
|  | **68.8(58.4 to 78.9)**  | **1.8(0.9 to 4.0)**  |

## Statistical Analysis

|  |  |  |
| --- | --- | --- |
| **Groups** | **LNP023 200mg b.i.d.,Anti-C5 antibody** |  |
|  **Type of Statistical Test**  | **Superiority** |  |
|  **P Value**  | **<0.0001** | **two sided unadjusted p-value** |
|  **Method**  | **Regression, Logistic** | **Logistic regression model using Firth** |
| **Odds Ratio (OR)** | **495.74** |  |
| **95% Confidence Interval2-Sided** | **24.41 to 10066.53** |  |

## Statistical Analysis

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| --- | --- | --- |
| **Groups** | **LNP023 200mg b.i.d.,Anti-C5 antibody** |  |
|  **Type of Statistical Test**  | **Superiority** |  |
| **OtherDiff. in marginal proportion** | **67.0** |  |
| **95% Confidence Interval2-Sided** | **56.4 to 76.9** |  |

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

|  |  |
| --- | --- |
| **Description** | **Patients with hematological response are those with ≥ 2g/dL increase in hemoglobin from baseline regardless of transfusions and patients with Hb ≥ 12g/dL regardless of transfusions.
Patients in the LNP023-LNP023 group received iptacopan from Day 1 to Day 336 (48 weeks) while patients in the anti-C5 antibody-LNP023 group received iptacopan from Day 169 to Day 336 (treatment extension period - 24 weeks).** |
| **Time Frame** | **Up to 48 weeks** |
| **Analysis Population Description** | **Combined Full Analysis Set: includes all patients randomized to LNP023 200 mg b.i.d and all patients randomized to anti-C5 treatment and who switched to LNP023 in the treatment extension period.** |

|  |  |  |
| --- | --- | --- |
|  | **LNP023 200mg b.i.d.** | **Anti-C5 antibody** |
| **Arm/Group Description**  | **Iptacopan 200mg b.i.d. hard gelatin capsule.
After 24 weeks of LNP023 200mg b.i.d. treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive an additional 24 weeks of LNP023 200mg b.i.d.** | **In the Randomized Treatment Period patients randomized to receive Anti-C5 antibody continued with the same stable regimen of Anti-C5 antibody therapy as they had received prior to randomization. For eculizumab (administered as intravenous infusion every 2 weeks), the maintenance dose was a fixed dose, whereas for ravulizumab (administered as intravenous infusion every 8 weeks), the maintenance dose was based on body weight. After 24 weeks of Anti-C5 antibody treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive 24 weeks of LNP023 200mg b.i.d.** |
|  **Number of Participants Analyzed [units: participants]** | **62** | **34** |
| **Percentage of patients meeting hematological response criterion after the start of LNP023 treatment(units: Percentage of participants)**  |
| **≥2 g/dL increase in Hb from baseline irrespective of RBC transfusions** | **86.4** | **72.4** |
| **Hb ≥12 g/dL irrespective of RBC transfusions** | **67.8** | **58.6** |

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

|  |  |
| --- | --- |
| **Description** | **Requiring RBC transfusions refers to any patient receiving transfusions or meeting protocol defined criteria (Hemoglobin level ≤ 9 g/dL with signs /and or symptoms of sufficient severity to warrant a transfusion or Hemoglobin of ≤ 7 g/dL, regardless of presence of clinical signs and/or symptoms).
Patients randomized to anti-C5 treatment switched to LNP023 (iptacopan) on Day 169 and were treated until Day 336 (treatment extension period).** |
| **Time Frame** | **Up to 48 weeks** |
| **Analysis Population Description** | **Combined Full Analysis Set: includes all patients randomized to LNP023 200 mg b.i.d and all patients randomized to anti-C5 treatment and who switched to LNP023 in the treatment extension period.** |

|  |  |  |
| --- | --- | --- |
|  | **LNP023 200mg b.i.d.** | **Anti-C5 antibody** |
| **Arm/Group Description**  | **Iptacopan 200mg b.i.d. hard gelatin capsule.
After 24 weeks of LNP023 200mg b.i.d. treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive an additional 24 weeks of LNP023 200mg b.i.d.** | **In the Randomized Treatment Period patients randomized to receive Anti-C5 antibody continued with the same stable regimen of Anti-C5 antibody therapy as they had received prior to randomization. For eculizumab (administered as intravenous infusion every 2 weeks), the maintenance dose was a fixed dose, whereas for ravulizumab (administered as intravenous infusion every 8 weeks), the maintenance dose was based on body weight. After 24 weeks of Anti-C5 antibody treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive 24 weeks of LNP023 200mg b.i.d.** |
|  **Number of Participants Analyzed [units: participants]** | **62** | **34** |
| **Number of patients not requiring RBC transfusions after the start of LNP023 treatment(units: Participants)**  | **Count of Participants (Not Applicable)** | **Count of Participants (Not Applicable)** |
| **Since Day 1 of LNP023 treatment** | **51
 (82.26%)**  | **31
 (91.18%)**  |
| **Since Day 14 of LNP023 treatment** | **57
 (91.94%)**  | **32
 (94.12%)**  |

## Change from baseline in Hemoglobin at Visit Day 336

|  |  |
| --- | --- |
| **Description** | **Patients randomized to anti-C5 treatment switched to LNP023 (iptacopan) on Day 169 and were treated until Day 336 (treatment extension period).** |
| **Time Frame** | **Baseline, Day 336** |
| **Analysis Population Description** | **Full Analysis Set (FAS): patients to whom study treatment had been assigned by randomization. Only participants with valid HB measurements at baseline and Day 336 were analyzed.** |

|  |  |  |
| --- | --- | --- |
|  | **LNP023 200mg b.i.d.** | **Anti-C5 antibody** |
| **Arm/Group Description**  | **Iptacopan 200mg b.i.d. hard gelatin capsule.
After 24 weeks of LNP023 200mg b.i.d. treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive an additional 24 weeks of LNP023 200mg b.i.d.** | **In the Randomized Treatment Period patients randomized to receive Anti-C5 antibody continued with the same stable regimen of Anti-C5 antibody therapy as they had received prior to randomization. For eculizumab (administered as intravenous infusion every 2 weeks), the maintenance dose was a fixed dose, whereas for ravulizumab (administered as intravenous infusion every 8 weeks), the maintenance dose was based on body weight. After 24 weeks of Anti-C5 antibody treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive 24 weeks of LNP023 200mg b.i.d.** |
|  **Number of Participants Analyzed [units: participants]** | **59** | **30** |
| **Change from baseline in Hemoglobin at Visit Day 336(units: g/dL)**  | **Mean (95% Confidence Interval)** | **Mean (95% Confidence Interval)** |
|  | **3.35(3.04 to 3.67)**  | **3.36(2.94 to 3.79)**  |

## Statistical Analysis

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| --- | --- | --- |
| **Groups** | **LNP023 200mg b.i.d.,Anti-C5 antibody** |  |
|  **Type of Statistical Test**  | **Other** |  |
| **OtherAdjusted mean difference** | **-0.01** |  |
| **95% Confidence Interval2-Sided** | **-0.53 to 0.51** |  |

## Change from baseline in FACIT-Fatigue questionnaire at Day 336

|  |  |
| --- | --- |
| **Description** | **The FACIT-Fatigue is a 13-item questionnaire with support for its validity and reliability in PNH that assesses patient self-reported fatigue and its impact on daily activities and function. All FACIT scales are scored so that a high score is better. As each of the 13 items of the FACIT-F Scale ranges from 0-4, the range of possible scores is 0-52, with 0 being the worst possible score and 52 the best.
Patients randomized to anti-C5 treatment switched to LNP023 (iptacopan) on Day 169 and were treated until Day 336 (treatment extension period).** |
| **Time Frame** | **Baseline, Day 336** |
| **Analysis Population Description** | **Full Analysis Set (FAS): patients to whom study treatment had been assigned by randomization. Only participants with valid FACIT-Fatigue scores at baseline and Day 336 were analyzed.** |

|  |  |  |
| --- | --- | --- |
|  | **LNP023 200mg b.i.d.** | **Anti-C5 antibody** |
| **Arm/Group Description**  | **Iptacopan 200mg b.i.d. hard gelatin capsule.
After 24 weeks of LNP023 200mg b.i.d. treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive an additional 24 weeks of LNP023 200mg b.i.d.** | **In the Randomized Treatment Period patients randomized to receive Anti-C5 antibody continued with the same stable regimen of Anti-C5 antibody therapy as they had received prior to randomization. For eculizumab (administered as intravenous infusion every 2 weeks), the maintenance dose was a fixed dose, whereas for ravulizumab (administered as intravenous infusion every 8 weeks), the maintenance dose was based on body weight. After 24 weeks of Anti-C5 antibody treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive 24 weeks of LNP023 200mg b.i.d.** |
|  **Number of Participants Analyzed [units: participants]** | **55** | **26** |
| **Change from baseline in FACIT-Fatigue questionnaire at Day 336(units: score on a scale)**  | **Mean (95% Confidence Interval)** | **Mean (95% Confidence Interval)** |
| **Day 336** | **9.80(8.04 to 11.56)**  | **10.96(8.58 to 13.34)**  |

## Statistical Analysis

|  |  |  |
| --- | --- | --- |
| **Groups** | **LNP023 200mg b.i.d.,Anti-C5 antibody** |  |
|  **Type of Statistical Test**  | **Other** |  |
| **OtherAdjusted mean difference** | **-1.17** |  |
| **95% Confidence Interval2-Sided** | **-4.01 to 1.68** |  |

## Number of patients with clinical breakthrough hemolysis (BTH) events

|  |  |
| --- | --- |
| **Description** | **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.** |
| **Time Frame** | **Up to 336 Days** |
| **Analysis Population Description** | **Full Analysis Set was used to calculate the number of participants with events in the randomized treatment period and the entire study: patients to whom study treatment had been assigned by randomization.
Combined Full Analysis Set was used to calculate the number of patients with events after the start of LNP023 treatment: includes all patients randomized to LNP023 200 mg b.i.d and all patients randomized to anti-C5 treatment and who switched to LNP023 in the treatment extension period.** |

|  |  |  |
| --- | --- | --- |
|  | **LNP023 200mg b.i.d.** | **Anti-C5 antibody** |
| **Arm/Group Description**  | **Iptacopan 200mg b.i.d. hard gelatin capsule.
After 24 weeks of LNP023 200mg b.i.d. treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive an additional 24 weeks of LNP023 200mg b.i.d.** | **In the Randomized Treatment Period patients randomized to receive Anti-C5 antibody continued with the same stable regimen of Anti-C5 antibody therapy as they had received prior to randomization. For eculizumab (administered as intravenous infusion every 2 weeks), the maintenance dose was a fixed dose, whereas for ravulizumab (administered as intravenous infusion every 8 weeks), the maintenance dose was based on body weight. After 24 weeks of Anti-C5 antibody treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive 24 weeks of LNP023 200mg b.i.d.** |
|  **Number of Participants Analyzed [units: participants]** | **62** | **35** |
| **Number of patients with clinical breakthrough hemolysis (BTH) events(units: Participants)**  | **Count of Participants (Not Applicable)** | **Count of Participants (Not Applicable)** |
| **Number of patients with at least one event in the randomized treatment period** | **2
 (3.23%)**  | **6
 (17.14%)**  |
| **Number of patients with at least one event after the start of LNP023 treatment** | **6
 (9.68%)**  | **1
 (2.94%)**  |
| **Number of patients with at least one event during the entire study** | **6
 (9.68%)**  | **7
 (20%)**  |

## Number of patients with Major Adverse Vascular Events

|  |  |
| --- | --- |
| **Description** | **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.
A patient with multiple occurrences of an event under one treatment is counted only once for that treatment.
LNP023-LNP023 group (336 days) was exposed to longer duration of iptacopan treatment than the anti-C5-antibody-LNP023 group (168 days).** |
| **Time Frame** | **Up to 336 days** |
| **Analysis Population Description** | **Full Analysis Set was used to calculate the number of participants with events in the randomized treatment period: patients to whom study treatment had been assigned by randomization.
Combined Full Analysis Set was used to calculate the number of patients with events after the start of LNP023 treatment: includes all patients randomized to LNP023 200 mg b.i.d and all patients randomized to anti-C5 treatment and who switched to LNP023 in the treatment extension period.** |

|  |  |  |
| --- | --- | --- |
|  | **LNP023 200mg b.i.d.** | **Anti-C5 antibody** |
| **Arm/Group Description**  | **Iptacopan 200mg b.i.d. hard gelatin capsule.
After 24 weeks of LNP023 200mg b.i.d. treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive an additional 24 weeks of LNP023 200mg b.i.d.** | **In the Randomized Treatment Period patients randomized to receive Anti-C5 antibody continued with the same stable regimen of Anti-C5 antibody therapy as they had received prior to randomization. For eculizumab (administered as intravenous infusion every 2 weeks), the maintenance dose was a fixed dose, whereas for ravulizumab (administered as intravenous infusion every 8 weeks), the maintenance dose was based on body weight. After 24 weeks of Anti-C5 antibody treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive 24 weeks of LNP023 200mg b.i.d.** |
|  **Number of Participants Analyzed [units: participants]** | **62** | **35** |
| **Number of patients with Major Adverse Vascular Events(units: participants)**  | **Count of Participants (Not Applicable)** | **Count of Participants (Not Applicable)** |
| **Number of patients with at least one event in the randomized treatment period** | **1
 (1.61%)**  | **0
 (%)**  |
| **Number of patients with at least one event after the start of LNP023 treatment** | **2
 (3.23%)**  | **1
 (2.94%)**  |

## Adjusted annualized clinical BTH rate after the start of LNP023 treatment

|  |  |
| --- | --- |
| **Description** | **This endpoint is considering clinical BTH events after the start of LNP023 treatment. Therefore, results are presented in a single arm on LNP023 since it includes all patients in the Combined Full analysis set.
Adjusted annualized rate of clinical breakthrough hemolysis (BTH) events are from negative binomial model. A patient with multiple occurrences of an event under one treatment is counted only once for that treatment.The breakthrough is defined clinical if either there is a decrease in hemoglobin levels equal to or more than 2 g/dL (compared to the latest assessment, or within 15 days) or if patients present signs or symptoms of gross hemoglobinuria, painful crisis, dysphagia or any other significant clinical PNH-related signs & symptoms, in presence of laboratory evidence of intravascular hemolysis.** |
| **Time Frame** | **Up to 336 Days** |
| **Analysis Population Description** | **Combined Full Analysis Set: Includes all patients randomized to LNP023 200 mg b.i.d and all patients randomized to anti-C5 treatment and who switched to LNP023 in the treatment extension period** |

|  |  |
| --- | --- |
|  | **Overall LNP023 200 mg b.i.d during the entire study** |
| **Arm/Group Description**  | **Includes all patients randomized to LNP023 200 mg b.i.d and all patients randomized to anti-C5 treatment and who switched to LNP023 in the treatment extension period** |
|  **Number of Participants Analyzed [units: participants]** | **96** |
| **Adjusted annualized clinical BTH rate after the start of LNP023 treatment(units: BTH events/year)**  | **Number (95% Confidence Interval)** |
|  | **0.11(0.05 to 0.23)**  |

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

|  |  |
| --- | --- |
| **Description** | **This endpoint is considering clinical BTH events after the start of LNP023 treatment. Therefore, results are presented in a single arm on LNP023 since it includes all patients in the Combined Full analysis set.
Adjusted annualized Major Adverse Vascular Events (MAVEs incl. thrombosis) rate. A MAVE is defined as: acute peripheral vascular occlusion, amputation (non-traumatic; nondiabetic), cerebral arterial occlusion/cerebrovascular accident, cerebral venous occlusion, dermal thrombosis, gangrene (non-traumatic; nondiabetic), hepatic/portal vein thrombosis (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.
A patient with multiple occurrences of an event under one treatment is counted only once for that treatment.** |
| **Time Frame** | **Up to 336 Days** |
| **Analysis Population Description** | **Combined Full Analysis Set: Includes all patients randomized to LNP023 200 mg b.i.d and all patients randomized to anti-C5 treatment and who switched to LNP023 in the treatment extension period** |

|  |  |
| --- | --- |
|  | **Overall LNP023 200 mg b.i.d during the entire study** |
| **Arm/Group Description**  | **Includes all patients randomized to LNP023 200 mg b.i.d and all patients randomized to anti-C5 treatment and who switched to LNP023 in the treatment extension period** |
|  **Number of Participants Analyzed [units: participants]** | **96** |
| **Adjusted annualized Major Adverse Vascular Events rate after the start of LNP023 treatment(units: MAVE events/year)**  | **Number (95% Confidence Interval)** |
|  | **0.04(0.01 to 0.13)**  |

# Secondary Outcome Result(s)

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

|  |  |
| --- | --- |
| **Description** | **Marginal proportion (expressed as percentages) of participants who did not require transfusions between Day 14 and Day 168. Requiring red blood cell transfusions refers to any patient receiving transfusions or meeting protocol defined criteria (Hemoglobin level ≤ 9 g/dL with signs /and or symptoms of sufficient severity to warrant a transfusion or Hemoglobin of ≤ 7 g/dL, regardless of presence of clinical signs and/or symptoms). The term ‘marginal proportion’ can be interpreted as the population average probability of being a responder for each treatment group. These values include adjustment for baseline covariates and missing data has also been taken into account.** |
| **Time Frame** | **Between Day 14 and Day 168** |
| **Analysis Population Description** | **Full Analysis Set (FAS): patients to whom study treatment had been assigned by randomization.** |

|  |  |  |
| --- | --- | --- |
|  | **LNP023 200mg b.i.d.** | **Anti-C5 antibody** |
| **Arm/Group Description**  | **Iptacopan 200mg b.i.d. hard gelatin capsule.
After 24 weeks of LNP023 200mg b.i.d. treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive an additional 24 weeks of LNP023 200mg b.i.d.** | **In the Randomized Treatment Period patients randomized to receive Anti-C5 antibody continued with the same stable regimen of Anti-C5 antibody therapy as they had received prior to randomization. For eculizumab (administered as intravenous infusion every 2 weeks), the maintenance dose was a fixed dose, whereas for ravulizumab (administered as intravenous infusion every 8 weeks), the maintenance dose was based on body weight. After 24 weeks of Anti-C5 antibody treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive 24 weeks of LNP023 200mg b.i.d.** |
|  **Number of Participants Analyzed [units: participants]** | **62** | **35** |
| **Marginal proportion (expressed as percentages) of participants who remain free from transfusions(units: Percentage of participants)**  | **Number (95% Confidence Interval)** | **Number (95% Confidence Interval)** |
|  | **94.8(88.1 to 100.0)**  | **25.9(11.6 to 42.4)**  |

## Statistical Analysis

|  |  |  |
| --- | --- | --- |
| **Groups** | **LNP023 200mg b.i.d.,Anti-C5 antibody** |  |
|  **Type of Statistical Test**  | **Superiority** |  |
|  **P Value**  | **<0.0001** | **two sided unadjusted p-value** |
|  **Method**  | **OtherConditional logistic regression** |  |
| **Odds Ratio (OR)** | **108.41** |  |
| **95% Confidence Interval2-Sided** | **17.25 to 681.24** |  |

## Statistical Analysis

|  |  |  |
| --- | --- | --- |
| **Groups** | **LNP023 200mg b.i.d.,Anti-C5 antibody** | **logistic regression model** |
|  **Type of Statistical Test**  | **Superiority** |  |
| **OtherDiff. in marginal proportion** | **68.9** |  |
| **95% Confidence Interval2-Sided** | **51.4 to 83.9** |  |

## Change from baseline in hemoglobin between Day 126 and 168

|  |  |
| --- | --- |
| **Description** | **Change from baseline in hemoglobin levels as mean of visits between Day 126 and Day 168.
For this analysis, in order to factor out the effect of transfusions, if a patient had a transfusion during the randomized treatment period, then the hemoglobin values 30 days following the transfusion were excluded and hemoglobin data were imputed.** |
| **Time Frame** | **Baseline and mean of visits between Day 126 and 168** |
| **Analysis Population Description** | **Full Analysis Set (FAS): patients to whom study treatment had been assigned by randomization.** |

|  |  |  |
| --- | --- | --- |
|  | **LNP023 200mg b.i.d.** | **Anti-C5 antibody** |
| **Arm/Group Description**  | **Iptacopan 200mg b.i.d. hard gelatin capsule.
After 24 weeks of LNP023 200mg b.i.d. treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive an additional 24 weeks of LNP023 200mg b.i.d.** | **In the Randomized Treatment Period patients randomized to receive Anti-C5 antibody continued with the same stable regimen of Anti-C5 antibody therapy as they had received prior to randomization. For eculizumab (administered as intravenous infusion every 2 weeks), the maintenance dose was a fixed dose, whereas for ravulizumab (administered as intravenous infusion every 8 weeks), the maintenance dose was based on body weight. After 24 weeks of Anti-C5 antibody treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive 24 weeks of LNP023 200mg b.i.d.** |
|  **Number of Participants Analyzed [units: participants]** | **62** | **35** |
| **Change from baseline in hemoglobin between Day 126 and 168(units: g/dL)**  | **Mean (95% Confidence Interval)** | **Mean (95% Confidence Interval)** |
|  | **3.60(3.33 to 3.88)**  | **-0.06(-0.45 to 0.34)**  |

## Statistical Analysis

|  |  |  |
| --- | --- | --- |
| **Groups** | **LNP023 200mg b.i.d.,Anti-C5 antibody** |  |
|  **Type of Statistical Test**  | **Superiority** |  |
|  **P Value**  | **<0.0001** | **two sided unadjusted p-value** |
|  **Method**  | **OtherMixed Model of Repeated Measures (MMRM)** |  |
| **OtherAdjusted mean diff.** | **3.66** |  |
| **95% Confidence Interval2-Sided** | **3.20 to 4.12** |  |

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

|  |  |
| --- | --- |
| **Description** | **The FACIT-Fatigue is a 13-item questionnaire with support for its validity and reliability in PNH that assesses patient self-reported fatigue and its impact on daily activities and function. All FACIT scales are scored so that a high score is better. As each of the 13 items of the FACIT-F Scale ranges from 0-4, the range of possible scores is 0-52, with 0 being the worst possible score and 52 the best.** |
| **Time Frame** | **Baseline, mean of visits between Day 126 and Day 168** |
| **Analysis Population Description** | **Full Analysis Set (FAS): patients to whom study treatment had been assigned by randomization. Only participants with valid FACIT-Fatigue scores at baseline and between day 126 and day 168 were analyzed.** |

|  |  |  |
| --- | --- | --- |
|  | **LNP023 200mg b.i.d.** | **Anti-C5 antibody** |
| **Arm/Group Description**  | **Iptacopan 200mg b.i.d. hard gelatin capsule.
After 24 weeks of LNP023 200mg b.i.d. treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive an additional 24 weeks of LNP023 200mg b.i.d.** | **In the Randomized Treatment Period patients randomized to receive Anti-C5 antibody continued with the same stable regimen of Anti-C5 antibody therapy as they had received prior to randomization. For eculizumab (administered as intravenous infusion every 2 weeks), the maintenance dose was a fixed dose, whereas for ravulizumab (administered as intravenous infusion every 8 weeks), the maintenance dose was based on body weight. After 24 weeks of Anti-C5 antibody treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive 24 weeks of LNP023 200mg b.i.d.** |
|  **Number of Participants Analyzed [units: participants]** | **62** | **33** |
| **Change from baseline in FACIT-Fatigue questionnaire in the Randomized Treatment Period(units: score on a scale)**  | **Mean (95% Confidence Interval)** | **Mean (95% Confidence Interval)** |
| **Mean of visits between Day 126 and Day 168** | **8.59(6.72 to 10.47)**  | **0.31(-2.20 to 2.81)**  |

## Statistical Analysis

|  |  |  |
| --- | --- | --- |
| **Groups** | **LNP023 200mg b.i.d.,Anti-C5 antibody** |  |
|  **Type of Statistical Test**  | **Superiority** |  |
|  **P Value**  | **<0.0001** | **two sided unadjusted p-value** |
|  **Method**  | **OtherMixed Model of Repeated Measures (MMRM)** |  |
| **Mean Difference (Net)** | **8.29** |  |
| **95% Confidence Interval2-Sided** | **5.28 to 11.29** |  |

## Change from baseline in absolute reticulocyte count in the randomized treatment period

|  |  |
| --- | --- |
| **Description** | **Change from baseline in absolute reticulocyte count as mean of visits between Day 126 and Day 168** |
| **Time Frame** | **Baseline and mean of visits between Day 126 and 168** |
| **Analysis Population Description** | **Full Analysis Set (FAS): patients to whom study treatment had been assigned by randomization.** |

|  |  |  |
| --- | --- | --- |
|  | **LNP023 200mg b.i.d.** | **Anti-C5 antibody** |
| **Arm/Group Description**  | **Iptacopan 200mg b.i.d. hard gelatin capsule.
After 24 weeks of LNP023 200mg b.i.d. treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive an additional 24 weeks of LNP023 200mg b.i.d.** | **In the Randomized Treatment Period patients randomized to receive Anti-C5 antibody continued with the same stable regimen of Anti-C5 antibody therapy as they had received prior to randomization. For eculizumab (administered as intravenous infusion every 2 weeks), the maintenance dose was a fixed dose, whereas for ravulizumab (administered as intravenous infusion every 8 weeks), the maintenance dose was based on body weight. After 24 weeks of Anti-C5 antibody treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive 24 weeks of LNP023 200mg b.i.d.** |
|  **Number of Participants Analyzed [units: participants]** | **62** | **35** |
| **Change from baseline in absolute reticulocyte count in the randomized treatment period(units: x10^9 cells/L)**  | **Mean (95% Confidence Interval)** | **Mean (95% Confidence Interval)** |
|  | **-115.81(-126.40 to -105.23)**  | **0.34(-13.04 to 13.72)**  |

## Statistical Analysis

|  |  |  |
| --- | --- | --- |
| **Groups** | **LNP023 200mg b.i.d.,Anti-C5 antibody** |  |
|  **Type of Statistical Test**  | **Superiority** |  |
|  **P Value**  | **<0.0001** | **two sided unadjusted p-value** |
|  **Method**  | **OtherMixed Model of Repeated Measures (MMRM)** |  |
| **Mean Difference (Net)** | **-116.15** |  |
| **95% Confidence Interval2-Sided** | **-132.04 to -100.26** |  |

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

|  |  |
| --- | --- |
| **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).** |
| **Time Frame** | **Baseline and mean of visits between Day 126 and 168** |
| **Analysis Population Description** | **Full Analysis Set (FAS): patients to whom study treatment had been assigned by randomization.** |

|  |  |  |
| --- | --- | --- |
|  | **LNP023 200mg b.i.d.** | **Anti-C5 antibody** |
| **Arm/Group Description**  | **Iptacopan 200mg b.i.d. hard gelatin capsule.
After 24 weeks of LNP023 200mg b.i.d. treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive an additional 24 weeks of LNP023 200mg b.i.d.** | **In the Randomized Treatment Period patients randomized to receive Anti-C5 antibody continued with the same stable regimen of Anti-C5 antibody therapy as they had received prior to randomization. For eculizumab (administered as intravenous infusion every 2 weeks), the maintenance dose was a fixed dose, whereas for ravulizumab (administered as intravenous infusion every 8 weeks), the maintenance dose was based on body weight. After 24 weeks of Anti-C5 antibody treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive 24 weeks of LNP023 200mg b.i.d.** |
|  **Number of Participants Analyzed [units: participants]** | **62** | **35** |
| **Ratio to baseline in log-transformed LDH in the randomized treatment period(units: ln(ratio))**  | **Geometric Mean (95% Confidence Interval)** | **Geometric Mean (95% Confidence Interval)** |
|  | **0.96(0.90 to 1.03)**  | **0.98(0.89 to 1.07)**  |

## Statistical Analysis

|  |  |  |
| --- | --- | --- |
| **Groups** | **LNP023 200mg b.i.d.,Anti-C5 antibody** |  |
|  **Type of Statistical Test**  | **Superiority** |  |
|  **P Value**  | **0.8361** | **two sided unadjusted p-value** |
|  **Method**  | **OtherMixed Model of Repeated Measures (MMRM)** |  |
| **OtherGeometric mean ratio** | **0.99** |  |
| **95% Confidence Interval2-Sided** | **0.89 to 1.10** |  |

## Adjusted annualized clinical BTH rate in the randomized treatment period

|  |  |
| --- | --- |
| **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.** |
| **Time Frame** | **Between Day 1 and Day 168** |
| **Analysis Population Description** | **Full Analysis Set (FAS): patients to whom study treatment had been assigned by randomization.** |

|  |  |  |
| --- | --- | --- |
|  | **LNP023 200mg b.i.d.** | **Anti-C5 antibody** |
| **Arm/Group Description**  | **Iptacopan 200mg b.i.d. hard gelatin capsule.
After 24 weeks of LNP023 200mg b.i.d. treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive an additional 24 weeks of LNP023 200mg b.i.d.** | **In the Randomized Treatment Period patients randomized to receive Anti-C5 antibody continued with the same stable regimen of Anti-C5 antibody therapy as they had received prior to randomization. For eculizumab (administered as intravenous infusion every 2 weeks), the maintenance dose was a fixed dose, whereas for ravulizumab (administered as intravenous infusion every 8 weeks), the maintenance dose was based on body weight. After 24 weeks of Anti-C5 antibody treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive 24 weeks of LNP023 200mg b.i.d.** |
|  **Number of Participants Analyzed [units: participants]** | **62** | **35** |
| **Adjusted annualized clinical BTH rate in the randomized treatment period(units: BTH events/year)**  | **Number (95% Confidence Interval)** | **Number (95% Confidence Interval)** |
|  | **0.07(0.02 to 0.31)**  | **0.67(0.26 to 1.72)**  |

## Statistical Analysis

|  |  |  |
| --- | --- | --- |
| **Groups** | **LNP023 200mg b.i.d.,Anti-C5 antibody** |  |
|  **Type of Statistical Test**  | **Superiority** |  |
|  **P Value**  | **0.01183** | **two sided unadjusted p-value** |
|  **Method**  | **OtherNegative binomial model** |  |
| **OtherRate ratio** | **0.10** |  |
| **95% Confidence Interval2-Sided** | **0.02 to 0.61** |  |

## Statistical Analysis

|  |  |  |
| --- | --- | --- |
| **Groups** | **LNP023 200mg b.i.d.,Anti-C5 antibody** |  |
|  **Type of Statistical Test**  | **Superiority** |  |
| **OtherRate difference** | **-0.60** |  |
| **95% Confidence Interval2-Sided** | **-1.24 to 0.04** |  |

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

|  |  |
| --- | --- |
| **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.

 A patient with multiple occurrences of an event under one treatment is counted only once for that treatment.** |
| **Time Frame** | **Between Day 1 and Day 168** |
| **Analysis Population Description** | **Full Analysis Set (FAS): patients to whom study treatment had been assigned by randomization.** |

|  |  |  |
| --- | --- | --- |
|  | **LNP023 200mg b.i.d.** | **Anti-C5 antibody** |
| **Arm/Group Description**  | **Iptacopan 200mg b.i.d. hard gelatin capsule.
After 24 weeks of LNP023 200mg b.i.d. treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive an additional 24 weeks of LNP023 200mg b.i.d.** | **In the Randomized Treatment Period patients randomized to receive Anti-C5 antibody continued with the same stable regimen of Anti-C5 antibody therapy as they had received prior to randomization. For eculizumab (administered as intravenous infusion every 2 weeks), the maintenance dose was a fixed dose, whereas for ravulizumab (administered as intravenous infusion every 8 weeks), the maintenance dose was based on body weight. After 24 weeks of Anti-C5 antibody treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive 24 weeks of LNP023 200mg b.i.d.** |
|  **Number of Participants Analyzed [units: participants]** | **62** | **35** |
| **Adjusted annualized Major Adverse Vascular Events rate in the randomized treatment period(units: MAVE events/year)**  | **Number (95% Confidence Interval)** | **Number (95% Confidence Interval)** |
|  | **0.03(0.00 to 0.25)**  | **0.00(0.00 to 0.00)**  |

## Statistical Analysis

|  |  |  |
| --- | --- | --- |
| **Groups** | **LNP023 200mg b.i.d.,Anti-C5 antibody** |  |
|  **Type of Statistical Test**  | **Superiority** |  |
|  **P Value**  | **0.31731** | **two sided unadjusted p-value** |
|  **Method**  | **OtherPoisson model** |  |
| **Otherrate difference** | **0.03** |  |
| **95% Confidence Interval2-Sided** | **-0.03 to 0.10** |  |

# Other Pre-Specified Outcome Result(s)

## Change from baseline in absolute reticulocyte count at Day 336

|  |  |
| --- | --- |
| **Description** | **Change from baseline in absolute reticulocyte count at visit Day 336.
Patients randomized to anti-C5 antibody were switched to LNP023 (iptacopan) on Day 169 and were treated until Day 336 (treatment extension period).** |
| **Time Frame** | **Baseline and Day 336** |
| **Analysis Population Description** | **Full Analysis Set (FAS): patients to whom study treatment had been assigned by randomization. Only participants with valid absolute reticulocyte count at baseline and Day 336 were analyzed.** |

|  |  |  |
| --- | --- | --- |
|  | **LNP023 200mg b.i.d.** | **Anti-C5 antibody** |
| **Arm/Group Description**  | **Iptacopan 200mg b.i.d. hard gelatin capsule.
After 24 weeks of LNP023 200mg b.i.d. treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive an additional 24 weeks of LNP023 200mg b.i.d.** | **In the Randomized Treatment Period patients randomized to receive Anti-C5 antibody continued with the same stable regimen of Anti-C5 antibody therapy as they had received prior to randomization. For eculizumab (administered as intravenous infusion every 2 weeks), the maintenance dose was a fixed dose, whereas for ravulizumab (administered as intravenous infusion every 8 weeks), the maintenance dose was based on body weight. After 24 weeks of Anti-C5 antibody treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive 24 weeks of LNP023 200mg b.i.d.** |
|  **Number of Participants Analyzed [units: participants]** | **57** | **30** |
| **Change from baseline in absolute reticulocyte count at Day 336(units: x10^9 cells/L)**  | **Mean (95% Confidence Interval)** | **Mean (95% Confidence Interval)** |
|  | **-106.26(-117.57 to -94.96)**  | **-107.95(-123.18 to -92.73)**  |

## Statistical Analysis

|  |  |  |
| --- | --- | --- |
| **Groups** | **LNP023 200mg b.i.d.,Anti-C5 antibody** |  |
|  **Type of Statistical Test**  | **Other** |  |
| **OtherAdjusted mean difference** | **1.69** |  |
| **95% Confidence Interval2-Sided** | **-16.86 to 20.23** |  |

## Ratio to baseline in log-transformed LDH at Visit Day 336

|  |  |
| --- | --- |
| **Description** | **Average of the Lactate dehydrogenase (LDH) log transformed ratio to baseline at visit Day 336.The log transformation used refers to the natural log (base of e).
Patients randomized to anti-C5 treatment switched to LNP023 (iptacopan) on Day 169 and were treated until Day 336 (treatment extension period).** |
| **Time Frame** | **Baseline and Day 336** |
| **Analysis Population Description** | **Full Analysis Set (FAS): patients to whom study treatment had been assigned by randomization. Only participants with valid LDH measurements at baseline and Day 336 were analyzed.** |

|  |  |  |
| --- | --- | --- |
|  | **LNP023 200mg b.i.d.** | **Anti-C5 antibody** |
| **Arm/Group Description**  | **Iptacopan 200mg b.i.d. hard gelatin capsule.
After 24 weeks of LNP023 200mg b.i.d. treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive an additional 24 weeks of LNP023 200mg b.i.d.** | **In the Randomized Treatment Period patients randomized to receive Anti-C5 antibody continued with the same stable regimen of Anti-C5 antibody therapy as they had received prior to randomization. For eculizumab (administered as intravenous infusion every 2 weeks), the maintenance dose was a fixed dose, whereas for ravulizumab (administered as intravenous infusion every 8 weeks), the maintenance dose was based on body weight. After 24 weeks of Anti-C5 antibody treatment in the Randomized Treatment Period, participants had the option to enter the Extension Treatment Period to receive 24 weeks of LNP023 200mg b.i.d.** |
|  **Number of Participants Analyzed [units: participants]** | **61** | **33** |
| **Ratio to baseline in log-transformed LDH at Visit Day 336(units: ln(ratio))**  | **Geometric Mean (95% Confidence Interval)** | **Geometric Mean (95% Confidence Interval)** |
|  | **1.11(1.02 to 1.22)**  | **0.99(0.88 to 1.11)**  |

## Statistical Analysis

|  |  |  |
| --- | --- | --- |
| **Groups** | **LNP023 200mg b.i.d.,Anti-C5 antibody** |  |
|  **Type of Statistical Test**  | **Other** |  |
| **OtherGeometric mean ratio** | **1.12** |  |
| **95% Confidence Interval2-Sided** | **0.97 to 1.30** |  |

# Post-Hoc Outcome Result(s)

No data identified.

# Safety Results

|  |  |
| --- | --- |
|  **Time Frame**  | Adverse events of LNP023 group were reported from first dose of study treatment until the end of study treatment plus 30 days, up to a maximum duration of 48 weeks |
|  **Additional Description**  | Adverse events of anti-C5 antibody were reported from the date of first administration of anti-C5 study treatment in the randomized treatment period to the date of the last actual administration of anti-C5 antibody in the randomized treatment period. |
|  **Source Vocabulary for Table Default**  | MedDRA (25.1) |
|  **Collection Approach for Table Default**  | Systematic Assessment |

## All-Cause Mortality

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **LNP023 200mg b.i.d. (Randomized treatment period)N = 62** | **Anti-C5 antibody (Randomized treatment period)N = 35** | **LNP023 200mg b.i.d. (Randomized treatment period + extension treatment period)N = 62** | **Any LNP023 200mg b.i.d. (Randomized treatment period + extension treatment period)N = 96** |
|  **Arm/Group Description**  | Patients who were randomized to LNP023 200mg b.i.d. (time frame is up to week 24) | Patients who were randomized to Anti-C5 antibody (time frame is up to week 24) | Patients who were randomized LNP023 200mg b.i.d. (time frame is up to week 48) | Patients who were randomized to LNP023 200mg b.i.d. and patients who switched from Anti-C5 antibody to LNP023 200mg b.i.d. (time frame is up to 48 weeks) |
|  **Total Number Affected**  | 0 | 0 | 0 | 0 |
|  **Total Number At Risk**  | 62 | 35 | 62 | 96 |

## Serious Adverse Events

|  |  |
| --- | --- |
|  **Time Frame**  | Adverse events of LNP023 group were reported from first dose of study treatment until the end of study treatment plus 30 days, up to a maximum duration of 48 weeks |
|  **Additional Description**  | Adverse events of anti-C5 antibody were reported from the date of first administration of anti-C5 study treatment in the randomized treatment period to the date of the last actual administration of anti-C5 antibody in the randomized treatment period. |
|  **Source Vocabulary for Table Default**  | MedDRA (25.1) |
|  **Collection Approach for Table Default**  | Systematic Assessment |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **LNP023 200mg b.i.d. (Randomized treatment period)N = 62** | **Anti-C5 antibody (Randomized treatment period)N = 35** | **LNP023 200mg b.i.d. (Randomized treatment period + extension treatment period)N = 62** | **Any LNP023 200mg b.i.d. (Randomized treatment period + extension treatment period)N = 96** |
|  **Arm/Group Description**  | Patients who were randomized to LNP023 200mg b.i.d. (time frame is up to week 24) | Patients who were randomized to Anti-C5 antibody (time frame is up to week 24) | Patients who were randomized LNP023 200mg b.i.d. (time frame is up to week 48) | Patients who were randomized to LNP023 200mg b.i.d. and patients who switched from Anti-C5 antibody to LNP023 200mg b.i.d. (time frame is up to 48 weeks) |
|  **Total # Affected by any Serious Adverse Event**  | 6 | 5 | 9 | 13 |
|  **Total # at Risk by any Serious Adverse Event**  | 62 | 35 | 62 | 96 |
| **Blood and lymphatic system disorders** |     |     |     |     |
| **Breakthrough haemolysis** | 0 (0.00%) | 1 (2.86%) | 0 (0.00%) | 0 (0.00%) |
| **Extravascular haemolysis** | 0 (0.00%) | 1 (2.86%) | 0 (0.00%) | 0 (0.00%) |
| **Cardiac disorders** |     |     |     |     |
| **Sinus node dysfunction** | 1 (1.61%) | 0 (0.00%) | 1 (1.61%) | 1 (1.04%) |
| **Gastrointestinal disorders** |     |     |     |     |
| **Pancreatolithiasis** | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (1.04%) |
| **Hepatobiliary disorders** |     |     |     |     |
| **Jaundice** | 0 (0.00%) | 1 (2.86%) | 0 (0.00%) | 0 (0.00%) |
| **Portal vein thrombosis** | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (1.04%) |
| **Infections and infestations** |     |     |     |     |
| **Arthritis bacterial** | 0 (0.00%) | 1 (2.86%) | 0 (0.00%) | 0 (0.00%) |
| **Cellulitis** | 0 (0.00%) | 0 (0.00%) | 1 (1.61%) | 1 (1.04%) |
| **COVID-19** | 1 (1.61%) | 2 (5.71%) | 1 (1.61%) | 1 (1.04%) |
| **Intervertebral discitis** | 0 (0.00%) | 1 (2.86%) | 0 (0.00%) | 0 (0.00%) |
| **Pseudomonal sepsis** | 0 (0.00%) | 1 (2.86%) | 0 (0.00%) | 0 (0.00%) |
| **Pyelonephritis** | 1 (1.61%) | 0 (0.00%) | 1 (1.61%) | 1 (1.04%) |
| **Septic shock** | 0 (0.00%) | 0 (0.00%) | 1 (1.61%) | 1 (1.04%) |
| **Systemic infection** | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (1.04%) |
| **Urinary tract infection pseudomonal** | 1 (1.61%) | 0 (0.00%) | 1 (1.61%) | 1 (1.04%) |
| **Investigations** |     |     |     |     |
| **Influenza A virus test positive** | 0 (0.00%) | 1 (2.86%) | 0 (0.00%) | 0 (0.00%) |
| **Platelet count decreased** | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (1.04%) |
| **Musculoskeletal and connective tissue disorders** |     |     |     |     |
| **Rhabdomyolysis** | 1 (1.61%) | 0 (0.00%) | 1 (1.61%) | 1 (1.04%) |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** |     |     |     |     |
| **Basal cell carcinoma** | 1 (1.61%) | 0 (0.00%) | 1 (1.61%) | 1 (1.04%) |
| **Myelodysplastic syndrome** | 1 (1.61%) | 0 (0.00%) | 1 (1.61%) | 1 (1.04%) |
| **Nervous system disorders** |     |     |     |     |
| **Transient ischaemic attack** | 1 (1.61%) | 0 (0.00%) | 1 (1.61%) | 1 (1.04%) |
| **Renal and urinary disorders** |     |     |     |     |
| **Acute kidney injury** | 0 (0.00%) | 1 (2.86%) | 0 (0.00%) | 0 (0.00%) |
| **Bilirubinuria** | 0 (0.00%) | 1 (2.86%) | 0 (0.00%) | 0 (0.00%) |
| **Reproductive system and breast disorders** |     |     |     |     |
| **Ovarian cyst** | 0 (0.00%) | 0 (0.00%) | 1 (1.61%) | 1 (1.04%) |

## Other (Not Including Serious) Adverse Events

|  |  |
| --- | --- |
|  **Time Frame**  | Adverse events of LNP023 group were reported from first dose of study treatment until the end of study treatment plus 30 days, up to a maximum duration of 48 weeks |
|  **Additional Description**  | Adverse events of anti-C5 antibody were reported from the date of first administration of anti-C5 study treatment in the randomized treatment period to the date of the last actual administration of anti-C5 antibody in the randomized treatment period. |
|  **Source Vocabulary for Table Default**  | MedDRA (25.1) |
|  **Collection Approach for Table Default**  | Systematic Assessment |

|  |  |
| --- | --- |
| **Frequent Event Reporting Threshold** | 5%
  |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **LNP023 200mg b.i.d. (Randomized treatment period)N = 62** | **Anti-C5 antibody (Randomized treatment period)N = 35** | **LNP023 200mg b.i.d. (Randomized treatment period + extension treatment period)N = 62** | **Any LNP023 200mg b.i.d. (Randomized treatment period + extension treatment period)N = 96** |
|  **Arm/Group Description**  | Patients who were randomized to LNP023 200mg b.i.d. (time frame is up to week 24) | Patients who were randomized to Anti-C5 antibody (time frame is up to week 24) | Patients who were randomized LNP023 200mg b.i.d. (time frame is up to week 48) | Patients who were randomized to LNP023 200mg b.i.d. and patients who switched from Anti-C5 antibody to LNP023 200mg b.i.d. (time frame is up to 48 weeks) |
|  **Total # Affected by any Other Adverse Event**  | 34 | 21 | 43 | 62 |
|  **Total # at Risk by any Other Adverse Event**  | 62 | 35 | 62 | 96 |
| **Blood and lymphatic system disorders** |     |     |     |     |
| **Breakthrough haemolysis** | 2 (3.23%) | 6 (17.14%) | 6 (9.68%) | 7 (7.29%) |
| **Thrombocytopenia** | 3 (4.84%) | 0 (0.00%) | 3 (4.84%) | 5 (5.21%) |
| **Gastrointestinal disorders** |     |     |     |     |
| **Abdominal pain** | 4 (6.45%) | 1 (2.86%) | 5 (8.06%) | 5 (5.21%) |
| **Diarrhoea** | 9 (14.52%) | 2 (5.71%) | 10 (16.13%) | 12 (12.50%) |
| **Nausea** | 6 (9.68%) | 1 (2.86%) | 8 (12.90%) | 11 (11.46%) |
| **Vomiting** | 2 (3.23%) | 1 (2.86%) | 2 (3.23%) | 5 (5.21%) |
| **General disorders and administration site conditions** |     |     |     |     |
| **Pyrexia** | 2 (3.23%) | 3 (8.57%) | 4 (6.45%) | 5 (5.21%) |
| **Infections and infestations** |     |     |     |     |
| **COVID-19** | 4 (6.45%) | 7 (20.00%) | 17 (27.42%) | 25 (26.04%) |
| **Nasopharyngitis** | 7 (11.29%) | 3 (8.57%) | 9 (14.52%) | 12 (12.50%) |
| **Sinusitis** | 2 (3.23%) | 3 (8.57%) | 3 (4.84%) | 3 (3.13%) |
| **Upper respiratory tract infection** | 2 (3.23%) | 3 (8.57%) | 3 (4.84%) | 4 (4.17%) |
| **Urinary tract infection** | 4 (6.45%) | 1 (2.86%) | 7 (11.29%) | 7 (7.29%) |
| **Investigations** |     |     |     |     |
| **Blood lactate dehydrogenase increased** | 4 (6.45%) | 3 (8.57%) | 6 (9.68%) | 6 (6.25%) |
| **Musculoskeletal and connective tissue disorders** |     |     |     |     |
| **Arthralgia** | 5 (8.06%) | 1 (2.86%) | 7 (11.29%) | 7 (7.29%) |
| **Back pain** | 3 (4.84%) | 2 (5.71%) | 3 (4.84%) | 3 (3.13%) |
| **Nervous system disorders** |     |     |     |     |
| **Dizziness** | 4 (6.45%) | 0 (0.00%) | 4 (6.45%) | 4 (4.17%) |
| **Headache** | 11 (17.74%) | 1 (2.86%) | 12 (19.35%) | 14 (14.58%) |
| **Psychiatric disorders** |     |     |     |     |
| **Insomnia** | 3 (4.84%) | 0 (0.00%) | 4 (6.45%) | 4 (4.17%) |
| **Vascular disorders** |     |     |     |     |
| **Hypertension** | 3 (4.84%) | 0 (0.00%) | 4 (6.45%) | 6 (6.25%) |

# Other Relevant Findings

Not applicable

# Conclusion:

* The APPLY-PNH study enrolled a representative population of adult PNH patients with residual anemia despite receiving a stable regimen of standard of care anti-C5 therapy (eculizumab/ravulizumab). Iptacopan monotherapy at a dose of 200 mg b.i.d. was superior to Standard of Care anti-C5 therapy on the two primary hematological response endpoints and the majority of the secondary endpoints during the randomized treatment period.
* Continued treatment with iptacopan monotherapy 200 mg b.i.d over a total of 48 weeks provided durable treatment benefits by good hemolysis control with sustained and clinically meaningful increases in hemoglobin, the majority of patients having normal / near-normal hemoglobin levels ≥ 12 g/dL irrespective of transfusions at the end of the study, transfusion avoidance in most patients and sustained improvement of patient-reported fatigue.Patients switching from anti-C5 antibody treatment to iptacopan monotherapy 200 mg b.i.d. for 24 weeks had similar treatment benefits with clinically meaningful increases in hemoglobin, the majority of patients achieving normal / near-normal hemoglobin levels ≥ 12 g/dL irrespective of transfusions at the end of the study, transfusion avoidance and improvement of patient-reported fatigue.
* Iptacopan monotherapy was well tolerated with an acceptable safety profile over the 48- week study.

# Given the sustained efficacy shown with iptacopan monotherapy treatment for 48 weeks and the continued favorable safety profile over 48 weeks, this study continues to support a positive risk benefit assessment in the treatment of adult patients with PNH.

# Date of Clinical Trial Report Primary Analysis

20 Dec 2023