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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Iptacopan

Trial Indication(s)

Paroxysmal nocturnal hemoglobinuria (PNH)

Protocol Number

CLNP023C12301

Protocol Title

A multicenter, single-arm, open-label trial to evaluate efficacy and safety of oral, twice daily iptacopan in adult PNH patients who are naive to complement inhibitor therapy

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase III

Study Start/End Dates

Study Start Date: July 19, 2021 (Actual)
Primary Completion Date: November 02, 2022 (Actual)
Study Completion Date: April 18, 2023 (Actual)

Reason for Termination (If applicable)

Not applicable

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Study Design/Methodology

Study CLNP023C12301 (APPOINT-PNH) was a multicenter, single-arm, open-label trial in adult PNH patients who are naive to complement inhibitor therapy (including anti-C5 antibody treatment).

This study comprised of 3 periods:
• Screening Period: Lasting up to 8 weeks
• Core Treatment Period: A 24-week single arm, open-label period
• Extension Treatment Period: A 24-week open-label, iptacopan treatment period followed by core treatment period.

This study enrolled PNH patients with hemolysis (LDH > 1.5 ULN) and anemia (Hb <10 g/dL), who were naive to complement inhibitor therapy, including anti-C5 antibody treatment.

Centers

12 centers in 8 countries: France(1), United Kingdom(1), Italy(1), Korea, Republic of(1), Singapore(1), China(3), Malaysia(2), Germany(2)

Objectives:

Objectives of the Core Treatment Period:

Primary Objective:

The primary objective was to assess the effect of iptacopan on proportion of patients treated with iptacopan achieving a sustained increase from baseline in hemoglobin levels of ≥ 2 g/dL in the absence of RBC transfusion.

Secondary Objectives:

- To assess the effect of iptacopan on the proportion of patients achieving sustained hemoglobin levels ≥ 12 g/dL in the absence of red blood cell transfusions

- To assess the effect of iptacopan on transfusion avoidance (TA) defined as the proportion of patients who remain free from transfusions
- To assess the effect of iptacopan on average change in hemoglobin
- To assess the effect of iptacopan on average percent change in Lactate Dehydrogenase (LDH)
- To assess the effect of iptacopan on the rate of breakthrough hemolysis (BTH)
- To assess the effect of iptacopan on average change in reticulocyte counts
- To assess the effect of iptacopan on improving fatigue, using the FACIT-Fatigue questionnaire
- To assess the rates of Major Adverse Vascular Events (MAVEs incl. thrombosis)
- To assess safety and tolerability of iptacopan

Objectives of the Extension Treatment Period:

To assess long term safety, tolerability, and efficacy of iptacopan.

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

Iptacopan 200 mg b.i.d. orally

Statistical Methods

The analysis of all efficacy variables was based on the full analysis set (FAS) that included all patients with confirmed eligibility to whom study treatment was assigned.

Analysis of primary endpoint in the Core Treatment Period: The primary analysis of the primary endpoint was a logistic regression to estimate the response probability. The covariates in logistic regression included sex, age (indicator of age ≥ 45 years), an indicator variable of baseline hemoglobin ≥ 8 g/dL and an indicator of transfusion dependence (i.e., whether the patient had any transfusion in the last 6 months prior to starting study treatment). The results from protocol specified logistic regression method and 95% CI using bootstrap were computed. However, due to convergence issues, the estimates were obtained using simple proportion. The 95% CI using simple proportion were obtained using the bootstrap method.

Analysis of secondary endpoints in the Core Treatment Period:

For the Proportion of patients achieving sustained hemoglobin levels ≥ 12 g/dL in the absence of red blood cell transfusions and transfusion avoidance endpoints**, l**ogistic regression model was planned by considering the similar analysis approach

as primary analysis. Due to convergence issue, the proportion of responders was estimated using simple proportion as for the primary endpoint, with the 95% CI obtained using the bootstrap method.

For the Change from baseline in hemoglobin levels endpoint, if a patient had a transfusion during the core treatment period, then the hemoglobin values 30 days following the transfusion was considered missing and hemoglobin data was imputed.

The model for the estimation is a mixed model for repeated measures (MMRM) considering an unstructured covariance structure. The model included transfusion dependence, age (indicator of age ≥ 45 years), sex, visit, baseline hemoglobin, and the interactions between visits and baseline levels. The treatment estimates were computed as the mean changes from baseline corresponding to the average of hemoglobin levels measured in the last 6 weeks of treatment (that is the visits occurring between Day 126 and Day 168).

The treatment effect on percent change from baseline in LDH was assessed using a MMRM of log transformed ratio to baseline based on all observations collected during follow-up. The model for the estimation was a MMRM considering an unstructured covariance structure. The model included transfusion dependence, age (indicator of age ≥ 45 years), sex, visit, log-transformed baseline LDH and the interactions between visits and log-transformed baseline levels. Estimation was derived based on the average of the log transformed ratio from baseline estimated between Day 126 and Day 168. Percentage change from baseline and associated 95% confidence intervals was presented.

For the Rates of Major Adverse Vascular Events (MAVE) and Rates of clinical breakthrough hemolysis, analysis was planned to be carried out applying negative binomial model. Due to the zero events during core treatment, the rates of MAVE and clinical breakthrough hemolysis and 95% CI were estimated using the Wilson method.

The estimation of the change from baseline in absolute reticulocyte counts was derived from a MMRM. The model for the estimation was a MMRM considering an unstructured covariance structure. The model included transfusion dependence, age (indicator of age ≥ 45 years), sex, visit, baseline reticulocyte counts, and the interactions between visits and baseline levels. The estimation used the average of model derived estimates obtained at visits occurring between Day 126 and Day 168.

The model for the estimation of change from baseline in FACIT-Fatigue scores was a MMRM considering an unstructured covariance structure. The model included transfusion dependence, age (indicator of age ≥ 45 years), sex, visit, baseline in scores of fatigue, and the interactions between visits and baseline levels. The estimation was an average of treatment estimates derived for visits occurring between Day 126 and Day 168.

Analysis of endpoints in the Extension Treatment 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 full analysis set (FAS).

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 RBCs and WBCs clone size ≥ 10%
• Mean hemoglobin level <10 g/dL
• LDH > 1.5 x Upper Limit of Normal (ULN)
• Vaccination against Neisseria meningitidis infection is required prior to the start of study treatment
• If not received previously, vaccination against Streptococcus pneumoniae and Haemophilus influenzae infections should be given

Exclusion Criteria:
• Prior treatment with a complement inhibitor, including anti-C5 antibody
• Known or suspected hereditary complement deficiency
• History of hematopoietic stem cell transplantation
• Patients with laboratory evidence of bone marrow failure (reticulocytes <100x109/L; platelets <30x109/L; neutrophils <0.5x109/L).
• Active systemic bacterial, viral (incl. COVID-19)or fungal infection within 14 days prior to study drug administration.
• 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., dialysis), advanced cardiac disease (e.g., NYHA class IV heart failure), 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

Core treatment period

	LNP023	Total

Arm/Group Description	Participants receive LNP023 at a dose of 200 mg b.i.d. orally	
Started	40	40
Completed	40	40
Not Completed	0	0

Extension treatment period

	LNP023	**Total**
Arm/Group Description	Participants receive LNP023 at a dose of 200 mg b.i.d. orally	
Started	40	40
Completed	40	40
Not Completed	0	0

Baseline Characteristics

	LNP023	**Total**
Arm/Group Description	Participants receive LNP023 at a dose of 200 mg b.i.d. orally	
Number of Participants [units: participants]	40	40
Baseline Analysis Population Description		
Age Continuous (units: years) Analysis Population Type: Participants Mean ± Standard Deviation		
	42.1±15.85	

Sex: Female, Male (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)		
Female	17	17
Male	23	23
Race/Ethnicity, Customized (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)		
White	12	12
Black or African American	1	1
Asian	27	27

Primary Outcome Result(s)

Marginal Proportion (expressed as percentage) 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 of ≥ 2 g/dL on three out of four measurements between Day 126 and 168 of the core 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 of ≤9 g/dL (≤8 g/dL for Chinese population) with signs and or symptoms of sufficient severity to warrant a transfusion or Hemoglobin of ≤7 g/dL (≤6 g/dL for Chinese population), 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. Results incorporated a method to handle missing data using multiple imputation. Hence, all 40 patients enrolled contributed to the primary analysis.
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): All patients with confirmed eligibility to whom study treatment was assigned.

	LNP023
Arm/Group Description	Participants receive LNP023 at a dose of 200 mg b.i.d. orally
Number of Participants Analyzed [units: participants]	40
Marginal Proportion (expressed as percentage) 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)**
	92.2 (82.5 to 100.0)

Secondary Outcome Result(s)

Marginal proportion (expressed as percentage) 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 between Day 126 and 168 of the core 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 of ≤9 g/dL (≤8 g/dL for Chinese population) with signs and or symptoms of sufficient severity to warrant a transfusion or Hemoglobin of ≤7 g/dL (≤6 g/dL for Chinese population), 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. Results incorporated a method to handle missing data using multiple imputation. Hence, all 40 patients enrolled contributed to the analysis.
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): All patients with confirmed eligibility to whom study treatment was assigned.

	LNP023

Arm/Group Description	Participants receive LNP023 at a dose of 200 mg b.i.d. orally
Number of Participants Analyzed [units: participants]	40
Marginal proportion (expressed as percentage) with sustained hemoglobin levels of ≥ 12 g/dL in the absence of red blood cell transfusions (units: Percentage of responders)	**Number (95% Confidence Interval)**
	62.8 (47.5 to 77.5)

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

Description	Marginal proportion (expressed as percentage) of participants who did not require transfusions between Day 14 and Day 168. Requiring RBC transfusions refers to any patient receiving transfusions or meeting protocol defined criteria (Hemoglobin level of ≤9 g/dL (≤8 g/dL for Chinese population) with signs and or symptoms of sufficient severity to warrant a transfusion or Hemoglobin of ≤7 g/dL (≤6 g/dL for Chinese population), 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. The 95% CI was obtained using the bootstrap method
Time Frame	Between Day 14 and Day 168
Analysis Population Description	Full Analysis Set (FAS): All patients with confirmed eligibility to whom study treatment was assigned.

	LNP023
Arm/Group Description	Participants receive LNP023 at a dose of 200 mg b.i.d. orally
Number of Participants Analyzed [units: participants]	40
Marginal proportion (expressed as percentage) of participants who remain free from transfusions (units: Percentage of participants)	**Number (95% Confidence Interval)**
	97.6 (92.5 to 100.0)

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Change from baseline in hemoglobin levels in the core treatment period

Description	Change from baseline in hemoglobin levels as mean of visits between Day 126 and Day 168. In order to factor out the effect of transfusions in this analysis, if a patient had a transfusion during the core treatment period, the hemoglobin (Hb) values during 30 days following the transfusion were excluded and Hb data were imputed. Change from baseline was analyzed using a mixed model of repeated measures which included age (indicator variable of age ≥ 45 years), sex, history of transfusion (yes/no) prior to study treatment, visit, and baseline hemoglobin as fixed effects and the interaction between visit and baseline hemoglobin levels.
Time Frame	Baseline, Day 126 to 168
Analysis Population Description	Full Analysis Set (FAS): All patients with confirmed eligibility to whom study treatment was assigned.

	LNP023
Arm/Group Description	Participants receive LNP023 at a dose of 200 mg b.i.d. orally
Number of Participants Analyzed [units: participants]	40
Change from baseline in hemoglobin levels in the core treatment period (units: g/dL)	**Mean (95% Confidence Interval)**
	4.28 (3.87 to 4.70)

Percent change from baseline in LDH

Description	Percent change from baseline in lactate dehydrogenase (LDH) levels as mean of visits between Day 126 and Day 168. Percentage change from baseline was analyzed using a mixed model for repeated measures (MMRM) which includes age (indicator variable of age ≥ 45 years), sex, history of transfusion (yes/no) prior to study treatment, visit, baseline LDH as fixed effects and visit*baseline LDH as interaction. Results incorporated a method to handle missing data using multiple imputation. Hence, all 40 patients enrolled contributed to the analysis.
Time Frame	Baseline, Day 126 to 168
Analysis Population Description	Full Analysis Set (FAS): All patients with confirmed eligibility to whom study treatment was assigned.

	LNP023
Arm/Group Description	Participants receive LNP023 at a dose of 200 mg b.i.d. orally
Number of Participants Analyzed [units: participants]	40
Percent change from baseline in LDH (units: Percent change from baseline in LDH)	**Mean** **(95% Confidence Interval)**
	-83.55 (-84.90 to -82.08)

Adjusted annualized clinical BTH rate in the core treatment period

Description	Adjusted annualized rate of clinical breakthrough hemolysis (BTH) events is carried out using the Wilson method. 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): All patients with confirmed eligibility to whom study treatment was assigned.

	LNP023
Arm/Group Description	Participants receive LNP023 at a dose of 200 mg b.i.d. orally
Number of Participants Analyzed [units: participants]	40
Adjusted annualized clinical BTH rate in the core treatment period (units: BTH events/year)	**Number** **(95% Confidence Interval)**
	0.00 (0.00 to 0.17)

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Change from baseline in absolute reticulocyte count

Description	Change from baseline in absolute reticulocyte counts as mean of visits between Day 126 and Day 168. Change from baseline was analyzed using a MMRM which includes age (indicator variable of age ≥ 45 years), sex, history of transfusion (yes/no) prior to study treatment, visit, baseline reticulocyte counts as fixed effects and visit*baseline reticulocyte counts as interaction.
Time Frame	Baseline and mean of visits between Day 126 and 168
Analysis Population Description	Full Analysis Set (FAS): All patients with confirmed eligibility to whom study treatment was assigned.

	LNP023
Arm/Group Description	Participants receive LNP023 at a dose of 200 mg b.i.d. orally
Number of Participants Analyzed [units: participants]	40
Change from baseline in absolute reticulocyte count (units: x10^9 cells/L)	**Mean (95% Confidence Interval)**
	-82.48 (-89.33 to -75.62)

Change from baseline in FACIT-Fatigue score

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. Change from baseline was analyzed using a Mixed Model of Repeated Measures (MMRM) which includes age (indicator variable of age ≥ 45 years), sex, history of transfusion (yes/no) prior to study treatment, visit, baseline FACIT-Fatigue score as fixed effects and visit*baseline FACIT-Fatigue score as interaction.
Time Frame	Baseline and mean of visits between Day 126 and Day 168
Analysis Population Description	Full Analysis Set (FAS): All patients with confirmed eligibility to whom study treatment was assigned.

	LNP023
Arm/Group Description	Participants receive LNP023 at a dose of 200 mg b.i.d. orally
Number of Participants Analyzed [units: participants]	40
Change from baseline in FACIT-Fatigue score (units: score on a scale)	**Mean** **(95% Confidence Interval)**
	10.75 (8.66 to 12.84)

Adjusted annualized Major Adverse Vascular Events rate in the core treatment period

Description	Adjusted annual rate is carried out using the Wilson method. 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.
Time Frame	Between Day 1 and Day 168
Analysis Population Description	Full Analysis Set (FAS): All patients with confirmed eligibility to whom study treatment was assigned.

	LNP023
Arm/Group Description	Participants receive LNP023 at a dose of 200 mg b.i.d. orally
Number of Participants Analyzed [units: participants]	40
Adjusted annualized Major Adverse Vascular Events rate in the core treatment period (units: MAVE events/year)	**Number** **(95% Confidence Interval)**
	0.00 (0.00 to 0.17)

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Other Pre-Specified Outcome Result(s)

Percentage of patients meeting hematological response criteria irrespective of RBC transfusions

Description	Patients with hematological response are those with an increase in Hb from baseline ≥ 2g/dL irrespective of red blood cell (RBC) transfusions and patients achieving Hb ≥ 12g/dL irrespective of RBC transfusions.
Time Frame	Baseline, Day 336
Analysis Population Description	Full analysis set: All patients with confirmed eligibility to whom study treatment was assigned. Only participants with valid Hb measurements at Day 336 were analyzed.

	LNP023
Arm/Group Description	Participants receive LNP023 at a dose of 200 mg b.i.d. orally
Number of Participants Analyzed [units: participants]	39
Percentage of patients meeting hematological response criteria irrespective of RBC transfusions (units: Percentage of participants)	
≥2 g/dL increase in Hb from baseline irrespective of RBC transfusions	97.4
Hb ≥ 12g/dL irrespective of transfusions	79.5

Marginal Proportion (expressed as percentage) of patients not receiving and not requiring RBC transfusions

Description	Requiring Red Blood Cells (RBC) transfusions refers to any patient receiving transfusions or meeting protocol defined criteria (Hemoglobin level of ≤9 g/dL (≤8 g/dL for Chinese population) with signs and or symptoms of sufficient severity to warrant a transfusion or Hemoglobin of ≤7 g/dL (≤6 g/dL for Chinese population), regardless of presence of clinical signs and/or symptoms).
Time Frame	Between Day 14 and Day 336
Analysis Population Description	Full analysis set: All patients with confirmed eligibility to whom study treatment was assigned.

	LNP023
Arm/Group Description	Participants receive LNP023 at a dose of 200 mg b.i.d. orally
Number of Participants Analyzed [units: participants]	40
Marginal Proportion (expressed as percentage) of patients not receiving and not requiring RBC transfusions (units: Percentage of participants)	**Number** **(95% Confidence Interval)**
	97.5 (92.5 to 100.0)

Change from baseline in Hemoglobin levels

Description	Change from baseline in Hemoglobin at Visit Day 336
Time Frame	Baseline, Day 336
Analysis Population Description	Full analysis set: All patients with confirmed eligibility to whom study treatment was assigned. Only participants with valid Hb measurements at Day 336 were analyzed.

	LNP023
Arm/Group Description	Participants receive LNP023 at a dose of 200 mg b.i.d. orally
Number of Participants Analyzed [units: participants]	39
Change from baseline in Hemoglobin levels (units: g/dL)	**Mean** **± Standard Deviation**
Day 336	5.09 ± 2.010

Change from baseline in LDH at Visit Day 336

Description	Change from baseline in Lactate dehydrogenase (LDH) at Visit Day 336
Time Frame	Baseline, Day 336
Analysis Population Description	Full Analysis Set (FAS): All patients with confirmed eligibility to whom study treatment was assigned.

	LNP023
Arm/Group Description	Participants receive LNP023 at a dose of 200 mg b.i.d. orally
Number of Participants Analyzed [units: participants]	40
Change from baseline in LDH at Visit Day 336 (units: U/L)	**Mean ± Standard Deviation**
Day 336	−1393.3 ± 652.15

Adjusted annualized clinical BTH rate after the start of LNP023 treatment

Description	Adjusted annualized rate of clinical breakthrough hemolysis (BTH) events is carried out using the Wilson method. 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 336
Analysis Population Description	Full Analysis Set (FAS): All patients with confirmed eligibility to whom study treatment was assigned.

	LNP023
Arm/Group Description	Participants receive LNP023 at a dose of 200 mg b.i.d. orally

Number of Participants Analyzed [units: participants]	40
Adjusted annualized clinical BTH rate after the start of LNP023 treatment (units: BTH events/year)	**Number (95% Confidence Interval)**
	0.05 (0.01 to 0.17)

Change from baseline in absolute reticulocyte count at Day 336

Description	Change from baseline in absolute reticulocyte count at visit Day 336.
Time Frame	Baseline, Day 336
Analysis Population Description	Full Analysis Set (FAS): All patients with confirmed eligibility to whom study treatment was assigned. Only participants with valid absolute reticulocyte count measurements at baseline and Day 336 were analyzed.

	LNP023
Arm/Group Description	Participants receive LNP023 at a dose of 200 mg b.i.d. orally
Number of Participants Analyzed [units: participants]	39
Change from baseline in absolute reticulocyte count at Day 336 (units: x10^9 cells/L)	**Mean ± Standard Deviation**
	-76.55 ± 50.149

Change from baseline in FACIT-Fatigue score

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, Day 336

Analysis Population Description	Full Analysis Set (FAS): All patients with confirmed eligibility to whom study treatment was assigned. Only participants with valid FACIT-Fatigue scores at baseline and Day 336 were analyzed.

	LNP023
Arm/Group Description	Participants receive LNP023 at a dose of 200 mg b.i.d. orally
Number of Participants Analyzed [units: participants]	39
Change from baseline in FACIT-Fatigue score (units: score on a scale)	**Mean ± Standard Deviation**
	10.4 ± 10.14

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

Description	Adjusted annual rate is carried out using the Wilson method. A Major Adverse Vascular Events (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
Time Frame	Between Day 1 and Day 336
Analysis Population Description	Full Analysis Set (FAS): All patients with confirmed eligibility to whom study treatment was assigned.

	LNP023
Arm/Group Description	Participants receive LNP023 at a dose of 200 mg b.i.d. orally
Number of Participants Analyzed [units: participants]	40

Adjusted annualized Major Adverse Vascular Events rate after the start of LNP023 treatment (units: MAVE events/year)	**Number** **(95% Confidence Interval)**
	0.00 (0.00 to 0.09)

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 up to 30 days, up to a maximum duration of 48 weeks
Source Vocabulary for Table Default	MedDRA (26.0)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	LNP023 200mg b.i.d. **N = 40**
Arm/Group Description	LNP023 200mg b.i.d.
Total Number Affected	0
Total Number At Risk	40

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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 up to 30 days, up to a maximum duration of 48 weeks
Source Vocabulary for Table Default	MedDRA (26.0)
Collection Approach for Table Default	Systematic Assessment

	LNP023 200mg b.i.d. N = 40
Arm/Group Description	LNP023 200mg b.i.d.
Total # Affected by any Serious Adverse Event	8
Total # at Risk by any Serious Adverse Event	40
Blood and lymphatic system disorders	
Breakthrough haemolysis	1 (2.50%)
Eye disorders	
Cataract	1 (2.50%)
Infections and infestations	
COVID-19	2 (5.00%)
Infection	1 (2.50%)

Pneumonia	1 (2.50%)
Pneumonia bacterial	1 (2.50%)
Metabolism and nutrition disorders	
Type 2 diabetes mellitus	1 (2.50%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Malignant melanoma	1 (2.50%)

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 up to 30 days, up to a maximum duration of 48 weeks
Source Vocabulary for Table Default	MedDRA (26.0)
Collection Approach for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	LNP023 200mg b.i.d. N = 40
Arm/Group Description	LNP023 200mg b.i.d.

Total # Affected by any Other Adverse Event	24
Total # at Risk by any Other Adverse Event	40
Gastrointestinal disorders	
Abdominal pain	3 (7.50%)
Constipation	3 (7.50%)
Diarrhoea	6 (15.00%)
Vomiting	3 (7.50%)
General disorders and administration site conditions	
Pyrexia	3 (7.50%)
Infections and infestations	
COVID-19	7 (17.50%)
Upper respiratory tract infection	7 (17.50%)
Metabolism and nutrition disorders	
Iron deficiency	3 (7.50%)
Nervous system disorders	
Headache	12 (30.00%)

Other Relevant Findings

Not applicable

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Conclusion:

- The APPOINT-PNH study enrolled a representative population of adult PNH patients with clinically significant anemia and intravascular hemolysis, who were naive to complement inhibitor therapy, including anti-C5 antibody treatment. The study met the primary objective for the primary hematological response endpoint; the marginal proportion of patients achieving clinically meaningful improvement in hemoglobin during the core treatment period was 92.2% with the lower bound of the 95% confidence interval exceeding the predefined threshold of 15% by a factor of > 5-fold.
- Iptacopan 200 mg b.i.d. monotherapy provided continued and durable treatment benefits in the entire study by inhibiting intravascular hemolysis and preventing the emergence of extravascular hemolysis:
    - Nearly all patients achieved ≥ 2 g/dL increase in Hb from baseline irrespective of transfusions, with most patients achieving Hb ≥ 12g/dL at the end of the extension treatment period.
    - Nearly all patients did not require RBC transfusions.
    - A clinically relevant increase in mean Hb towards Hb normalization at the end of the core treatment period was sustained throughout the extension treatment period.
    - Improvement of patient-reported fatigue was maintained during the entire study.
- 48-week iptacopan monotherapy had a favorable safety profile and was well tolerated in PNH patients naive to complement inhibitor therapy.
- Overall, the sustained efficacy of iptacopan oral monotherapy treatment for 48 weeks and its continued favorable safety profile in this 48-week Phase III APPOINT-PNH study, support a positive benefit-risk assessment in the treatment of complement inhibition-naïve adult PNH patients.

Date of Clinical Trial Report Final Analysis

14 Dec 2023