NOVARTIS

Clinical Development

LNP023/Iptacopan

CLNP023C12301

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

Statistical Analysis Plan (SAP)

Document type:	SAP Documentation Amendment 2
Document status:	Final
Release date:	17-November-2022
Number of pages:	59

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
23-March-2022	SAP Amendment 1: Document finalized after study protocol V3 has been finalized and prior to Dry Run.	Additional details to help programing and for implementing the analysis	Clarification added for DMC report	Section 2.1
			Clarification added for study date for patients who never take treatment	Section 2.1.1.1
			Clarification added for baseline definition	Section 2.1.1.2
			Clarification added for last contact date	Section 2.1.1.5
			Clarification of screening set and enrolled set	Section 2.2
			Clarification added for patient disposition and medical history	Section 2.3
			Clarification added for definition of exposure, dose intensity, prior and concomitant medication	Sections 2.4.1, 2.4.2
			Clarification added for summary statistics	Section 2.5.2.1
			Handling of missing data for analysis of primary and secondary endpoints	Sections 2.5.3, 2.6.2, 5.2.2, 5.2.3
			[redacted]	Section 2.5.6.1
			Clarification on the analysis of secondary endpoints	[redacted] Table 5-1
			Tabular representation of estimands in order to use similar naming convention in TFL shells	Section 5.2.3.3 Section 2.7.1, 2.7.3

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Clarification on the convergence issue in MMRM Clafirication on safety	
		Analyses added	Threshold-based analysis was added Sensitivity analyses where missing central lab data will be replaced by available local lab data collected at the same visit Sensitivity analyses due to different transfusion criteria for Chinese patients Summary for historical lab parameters prior to screening CI for AEs and AESI CTCAE grading	Section 2.5.2.2, 3, 5.2.2.3 Sections 2.5.4, 2.6.3, 5.2.1, Table 5-1 Section 2.5.4, 5.2.1 Section 2.5.6.2 Sections 2.7, 2.7.1.1 Section 2.7.3
		Analyses changed	[redacted] Instead of compliance, summaries of interruptions are added Updated defintion of prior, concomitant and post treatment Instead of box plots, arithmetic mean(sd) plots for safety parameters, vital signs are added Instead of "at enrollment", "prior to	[redacted] Section 2.4.1 Section 2.4.2 Sections 2.7.3, 2.7.3.2 Section 4

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			starting study treatment" is used for indicator of transfusion dependency	
		Aligning with updates made to study protocol	Absolute reticulocytes counts at screening History of MAVE, transfusion history [redacted] Clarification on handling of transfusions Supplementary analysis on primary endpoints [redacted]	Section 1.1 Sections 1.1, 2.2.1, 2.3.2 [redacted] Sections 2.5.1, 2.6.1.2 Section 2.5.5 [redacted]
		Alignment with project level Master Analysis Plan	Safety analyses are aligned with those in the LNP023 project level MAP	Sections 2.7.1, 2.7.1.1, 2.7.3, 2.7.3.1, 2.7.3.2, 2.11
		Analyses detailed in separate statistical analysis plan for PROs	The analyses which are detailed in a separate SAP for PROs are removed from the document	Section 2.10
		Throughout the document inconsistencies and typos have been addressed		

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
16-November-2022	SAP Amendment 2: Addressing issues identified during programming for Dry Run	Approach defined for the primary analysis, in case zero cells across categories defined by the covariates lead to convergence issues	Added simple proportion Added details of statistical methods	Sections 2.5.2.2, 2.5.5, 2.5.6.1, 2.6.1.1, 2.6.1.2, 5.2.2.2
		The additional details address the analysis considerations for sparse data. The analyses for breakthrough hemolysis and MAVE (secondary endpoints) are aligned with those in protocol. The zero inflated models specified in previous versions of SAP lead to convergence issues and hence switching to protocol specified negative binomial model. Propose alternate methods for non-convergence	Added alternative models and model selection procedure	Sections 2.6.1.7, 2.6.1.8
		Definition for baseline hemoglobin is clarified, with respect to dealing with data from unplanned visits	Added more details for baseline hemoglobin and baseline PRO computation	Section 2.1.1.2

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		Clarity needed for baseline computation of certain PROs		
		Transfusion dependency should be prior to study treatment instead of prior to screening	Update transfusion dependency definition	Section 2.3.2
		Details needed for implementation of multiple imputation	Add more detail to multiple mutation model Add criteria to handle the case where imputed values are out of constrained range	Sections 2.5.3, 2.6.2
		The “indicator variable of baseline hemoglobin” should not be included in MMRM model since baseline (continuous) is already in the model	Remove “indicator variable of baseline hemoglobin”	Sections 2.6.1.3, 2.6.1.4, 2.6.1.5, 2.6.1.6,
		Present the geometric mean for LDH expressed as a % for alignment with protocol	Update to percentage change (reduction or increase) from baseline	Section 2.6.1.6
		More sensitivity and supportive analysis need to be added in this summary table.	Update Table 5-1	Section 5.2.1

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		Added sensitivity analysis to assess the robustness of handling missing hemoglobin data under different assumptions of missing signs and symptoms'	Add sensitivity analysis to address the issue	Section 2.5.4, 2.6.3
		The result based on treatment policy for primary analysis may be of interest The result based on hypothetical strategy for LDH, FACIT and reticulocytes may be of interest	Add additional supportive analysis	Section 2.6.4
		[redacted]		[redacted]
		China specific outputs will not include in global CSR	Move the sensitivity analysis regarding different transfusion criteria between Chinese patients and non-Chinese patients to China specific SAP	Sections 2.5.4, 2.5.6.2
		Current definition regarding prior, concomitant and post therapy need update in order to align with project level updates	Improve language	Section 2.4.2

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		Make method for calculation of exposure-adjusted incidence rate robust to low frequency count data	Update statistical models and improve the language	Sections 2.7.1, 2.7.1.1
		Added clarification regarding the approach to handle abnormal measurements Liver toxicity summary needed more detail	Improved the language and added more details	Section 2.7.3
		Thresholds needed for blood pressure and temperature	Added thresholds	Section 2.7.3,2
		Addressed typographical errors	Improve current language or remove the duplicated language	Sections 2.1, 2.4.1, 5.2.2, 5.2.3

Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse Event
AESI	Adverse event of special interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AR	Autoregressive
b.i.d.	Bis in die/twice a day
BP	Blood pressure
BTH	Breakthrough hemolysis
BUN	Blood Urea Nitrogen
COA	Clinical Outcome Assessment
COVID-19	Coronavirus disease-19
CRF	Case Report Form
CS	Compound Symmetry
CSR	Clinical Study Report
CTT	Clinical Trial Team
CV	Coefficient of variation
DHT	Dihydrotestosterone
DMC	Data Monitoring Committee
DMS	Document Management System
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
eCRS	Electronic Case Retrieval Strategy
[redacted]	[redacted]
EOS	End of Study
ePRO	Electronic Patient Reported Outcome
[redacted]	[redacted]
ES	Enrolled Set
eSAE	Electronic Serious Adverse Event
FAS	Full Analysis Set
FSH	Follicle Stimulating Hormone
h	Hour
Hb	Hemoglobin
HR	Heart rate
IA	Interim Analyses
ICF	Informed Consent Form
IND	Investigational New Drug
LDH	Lactate dehydrogenase
LH	Luteinizing hormone
LLOQ	Lower limit of quantification
MAR	Missing at random
MAVE	Major Adverse Vascular Events
MedDRA	Medical Dictionary for Drug Regulatory Affairs

mg	Milligram(s)
[redacted]	[redacted]
PNH	Paroxysmal nocturnal hemoglobinuria
[redacted]	[redacted]
pRBC	Packed Red blood cell transfusions
PRO	Patient-reported Outcomes
PT	Prothrombin time
PT	Preferred Term
PTA	Post-trial access
QTcF	QT interval corrected by Fridericia's formula
RAP	Reporting & Analysis Process
RBC	Red blood cell(s)
REP	Rollover extension program
[redacted]	[redacted]
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBP	Systolic blood pressure
sCR	Serum creatinine
SD	Standard deviation
SOC	System Organ Class
SoC	Standard of care
T3	Triiodothyronine
T4	Thyroxine
TA	Transfusion avoidance
TBL	Total bilirubin
TEAE	Treatment emergent adverse event
TFLs	Tables, Figures, Listings
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell(s)
WHO	World Health Organization

1 Introduction

The purpose of the document is to describe the statistical analyses to be included in the clinical study report (CSR) to be produced for submission at the time the last patient has completed the core treatment period in study CLNP023C12301. Hence the document covers the efficacy analysis on the core treatment period and the safety analysis on the data in the core treatment period, as well as the safety data in the extension treatment period collected till the data cut off for the submission of the CSR mentioned before.

An additional CSR will be produced when the last participant has completed the last visit in the extension treatment period, when the final study database has been locked. The statistical analyses for that CSR will be mentioned in a separate document.

1.1 Study design

Study CLNP023C12301 is 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 is comprised of three periods (see Figure 1-1):

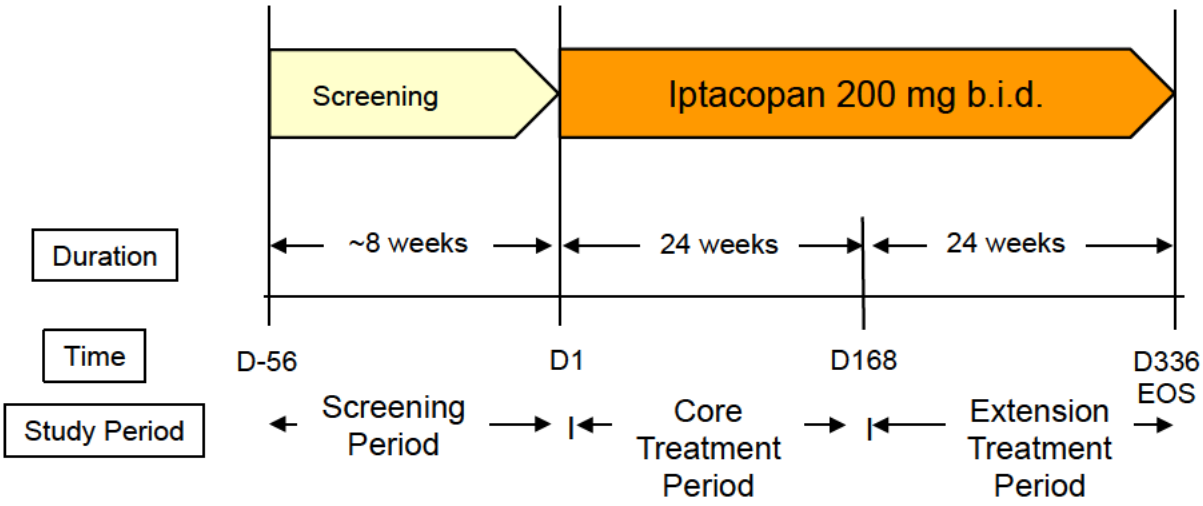
- A Screening period lasting up to 8 weeks (unless there is a need to extend it for vaccinations required for inclusion)
- A 24-week single arm, open-label Core treatment period for the primary efficacy and safety analysis
- A 24-week open-label, iptacopan treatment Extension period

This study will enroll PNH patients with hemolysis (LDH > 1.5 ULN) and anemia (hemoglobin <10 g/dL), who are naive to complement inhibitor therapy, including anti-C5 antibody treatment, with approximately 40% of all participants having received at least one (1) packed-RBC transfusion within 6 months prior to starting study treatment.

A total of approximately 40 participants will be starting study treatment in the trial. All participants must provide written informed consent prior to start of any study-related activities.

The study design is shown in the schematic below.

Figure 1-1 Study design



The database of the study will be locked for the Core treatment period when the last participant has completed the Day 168 visit in the study or end of study (EOS) for participants who discontinue from the study prior to the extension treatment period. The final database lock will take place when the last participant has completed the last visit (Day 336 or EOS) for the extension treatment period.

Screening

Screening period starts at the time of Informed Consent Form (ICF) signing and lasts until the day preceding Day 1 of the Core treatment period.

Participants will be asked to review and sign the ICF prior to starting the screening assessments. After signing the ICF, inclusion and exclusion criteria will be assessed to verify participants' eligibility for starting study treatment in the study. This will be followed by the visit's assessments as outlined in Table 8-1 of CLNP023C12301 clinical study protocol, as applicable.

By signing the ICF, the participants will provide access to the medical records including numbers of transfusions, unit numbers of packed-RBC received in the last 12 months prior to screening and history of Major Adverse Vascular Events (MAVEs).

Vaccinations should be completed as per Inclusion criteria (Section 5.1 in study protocol). To fulfill the hemoglobin and LDH eligibility criteria, participant will have two different samples collected during the screening period and tested by the central laboratory prior to starting study treatment. In case the participant has received a RBC transfusion following the initial Screening visit, the participant is eligible based on the initial central hemoglobin if < 10g/dL.

The absolute reticulocytes count will be measured at Screening to determine eligibility with regards to exclusion criterion # 6. Due to the kinetics of maturation of reticulocytes into mature red blood cells and turnaround time from reticulocytes sample collection and analysis by central laboratory, local reticulocytes testing can be performed at the same time as the central testing during the Screening period. In the event that the absolute reticulocytes count as assessed by the central laboratory during the Screening period is below the protocol defined threshold (absolute reticulocytes $<100x10^9/L$) and only in this scenario, the results from the local lab

testing can be used to determine participant's eligibility. The results of the local laboratory values (including reference ranges) should be included in the eCRF to document eligibility.

If eligibility criteria are not met due to any assessment, the participant should be considered as having failed the screening and cannot start study treatment. The participant can be re-screened as described in detail in Section 8.1 in study protocol.

Core treatment period

Participants who meet the eligibility criteria will proceed to the Core treatment period. Treatment with iptacopan at a dose of 200 mg b.i.d. will start on the first day (Day 1) and continue for 24 weeks with study visits and corresponding assessments according to the schedule described in Table 8-1 of CLNP023C12301 clinical study protocol.

The Core treatment period will end with the completion of the Week 24 visit assessments. Upon completion of the Week 24 visit, participants may enter the Extension treatment period, as described below.

Extension treatment period

Participants who benefit from treatment and are taking iptacopan at Week 24 visit (i.e. did not permanently discontinue study medication), will be offered to continue iptacopan treatment during the extension treatment period of 24 weeks with study visits and assessments according to schedule detailed in Table 8-2 of CLNP023C12301 clinical study protocol. For participants not agreeing to continue iptacopan treatment in the Extension treatment period after completing Day 168 visit, End of Study will be after completing recommended procedures defined in Section 9.1.1 of CLNP023C12301 clinical study protocol.

The extension treatment period will last 24 weeks. After completion of the extension treatment period, the participant will be able to join the Roll-over extension program, which will provide access to iptacopan and enable long-term safety monitoring. For participants not agreeing to continue in the Roll-over extension program after completing Day 336 visit, End of Study will be after completing recommended procedures defined in Section 9.1.1 of the study protocol.

1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints for the Core treatment period

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the effect of iptacopan on proportion of participants treated with iptacopan achieving a sustained increase from baseline in hemoglobin levels of ≥ 2 g/dL in the absence of red blood cell transfusion	• Response defined as having an increase from baseline in Hb ≥ 2 g/dL assessed between Day 126 and Day 168, in the absence of packed red blood cell (pRBC) transfusions between Day 14 and Day 168
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the effect of iptacopan on the proportion of participants achieving	• Response defined as having Hb levels ≥ 12 g/dL between Day 126 and Day 168 in

Objective(s)	Endpoint(s)
sustained hemoglobin levels ≥ 12 g/dL in the absence of red blood cell transfusions	absence of red blood cell transfusion between Day 14 and Day 168
• To assess the effect of iptacopan on transfusion avoidance (TA) defined as the proportion of participants who remain free from transfusions	• Absence of administration of packed-red blood cell transfusions between Day 14 and Day 168
• To assess the effect of iptacopan on average change in hemoglobin	• Change from baseline in hemoglobin (g/dL) as mean of visits between Day 126 and Day 168
• To assess the effect of iptacopan on average percent change in Lactate Dehydrogenase (LDH)	• Percent change from baseline in LDH levels (U/L) as mean of visits between Day 126 and Day 168
• To assess the effect of iptacopan on the rate of breakthrough hemolysis (BTH)	• Occurrences of breakthrough hemolysis reported between Day 1 and Day 168
• To assess the effect of iptacopan on average change in reticulocyte counts	• Change from baseline in reticulocyte counts (10^9/L) as mean of visits between Day 126 and Day 168
• To assess the effect of iptacopan on improving fatigue, using the FACIT-Fatigue questionnaire	• Change from baseline in FACIT-Fatigue scores as mean of visits between Day 126 and Day 168
• To assess the rates of Major Adverse Vascular Events (MAVEs incl. thrombosis)	• Occurrences of MAVEs occurring between Day 1 and Day 168
• To assess safety and tolerability of iptacopan	• Safety assessments (including adverse events/serious adverse events, safety laboratory parameters, vital signs etc.) between Day 1 and Day 168

Table 1-2 Objectives and related endpoints for the Extension treatment period

Objective(s)	Endpoint(s)
• To assess long term safety, tolerability and efficacy of iptacopan	• Safety assessments including adverse events/serious adverse events, safety laboratory parameters, vital signs etc. through End of Study visit • Efficacy endpoints including hematological response parameters, transfusion avoidance, BTH, FACIT-fatigue score, MAVEs through End of Study visit

1.2.1 Primary estimands

The primary clinical question of interest is:

What is the effect of iptacopan, regardless of discontinuations of study drug or occurrence of Breakthrough hemolysis (BTH) or Major Adverse Vascular Events (MAVEs) on the primary endpoint (a composite of improvement in hemoglobin levels and absence of RBC transfusions), as assessed by the proportion of responders?

This primary estimand captures both the hematological effect of the study drug (as evaluated by a clinically relevant increase of ≥ 2 g/dL in hemoglobin levels) and the absence of RBC transfusions after Day 14 which are regarded as treatment failure.

The attributes of the primary estimand are:

- Population: PNH Patients ≥ 18 years old with hemolysis (LDH > 1.5 ULN) and anemia (hemoglobin <10 g/dL), and who have not received any complement inhibitor therapy (including anti-C5 antibody).
- Treatment of interest: the investigational treatment iptacopan at a dose of 200 mg b.i.d regardless of whether the patient discontinues treatment (treatment policy).
- Intercurrent events: Transfusions (after Day 14) will be considered treatment failures and as such captured in the endpoint. Discontinuations of study medication for any reason, BTH events, and MAVEs will be handled with a treatment policy strategy.
- The summary measure: the probability of being a responder, standardized to the population of patients assigned to iptacopan in this study.

The justification of handling of intercurrent events is in Table 1-3. The overview of estimands and estimation methods is in Table 5-1 in Section 5.2.

Table 1-3 Justification of handling of intercurrent events

Intercurrent event	Handling strategy	Justification
Discontinuation of study medication	Treatment policy	The effect of treatment will be assessed even when participants discontinue study medication. Data collection will be maintained and available measurements post-treatment discontinuation used maintaining the treatment label as assigned at enrollment.
Breakthrough hemolysis events	Treatment policy	The effect of treatment will be assessed. Breakthrough hemolysis may affect the endpoints considered in the study, hence data collection will be maintained and available measurements collected after breakthrough hemolysis event keeping the treatment label as assigned at enrollment.
MAVEs	Treatment policy	The effect of treatment will be assessed, in particular in the presence or after the occurrence of MAVEs. Data collection will be maintained and available measurements collected after MAVEs used under the treatment assigned at enrollment.

1.2.2 Secondary estimands

The population associated with the secondary estimands is the same as for the primary estimands. For these secondary estimands we consider the same intercurrent events as for the primary estimands. The proposed approach in the case of transfusion handling will be described in the endpoint definition, while discontinuations of study medication, breakthrough hemolysis events, and MAVEs whose impact is expected to be reflected in the respective endpoints, will be handled with a treatment policy strategy.

The secondary estimands are defined by the evaluation of treatment effect on the following endpoints and summary measures:

- Response defined as having Hb levels ≥ 12 g/dL between Day 126 and Day 168 in absence of red blood cell transfusion between Day 14 and Day 168. The summary measure is the same as for the primary endpoint.
- Absence of administration of packed red blood cell transfusions (pRBC) between Day 14 and Day 168. Proportions of participants not receiving any transfusions between Day

14 and Day 168 (Transfusion Avoidance). The summary measure is the same as for the primary endpoint.

- Changes from baseline in hemoglobin between Day 126 and Day 168 where transfusions occurring between Day 14 and Day 168 are treated within a hypothetical strategy (as if the participants had not received any transfusions). The summary measure is the mean change from baseline in hemoglobin levels assessed between Day 126 and Day 168.
- Percent change from baseline in LDH between Day 126 and Day 168 where the strategy applied to transfusions is treatment policy. The summary measure is derived from the mean log transformed ratio to baseline in LDH between Day 126 and Day 168.
- Rates of BTH occurring between Day 1 and Day 168. The summary measure is occurrences per year.
- Change from baseline in reticulocytes counts between Day 126 and Day 168 where the strategy applied to transfusions is treatment policy. The summary measure is the mean change from baseline in reticulocytes counts assessed between Day 126 and Day 168.
- Change from baseline in scores of fatigue using the FACIT Fatigue questionnaire between Day 126 and Day 168, where the strategy applied to transfusions is treatment policy. The summary measure is the mean change from baseline in scores of fatigue assessed between Day 126 and Day 168.
- Rates of Major Adverse Vascular Events (MAVE) occurring between Day 1 and Day 168. The summary measure is occurrences per year.

Estimand considerations in case of COVID-19 pandemic impact

The overarching principle for primary and secondary estimands, is answering questions of treatment effect of iptacopan that are valid in conditions when the COVID-19 pandemic is no longer present.

Data capture and clinical evaluation activities include possible adaptations to restrictions for patient access to investigational sites in case of a new infection wave. The planned analyses could be supplemented by supportive analyses as well as sensitivity analyses if required by the presence of deviations from the normal methods of patient follow up and data capture.

Potential impact of a new wave of COVID-19 infections affecting measurements have been minimized through the measures proposed in the study protocol. However other impact that at this stage cannot be excluded such as withdrawal from study follow up due to infection which would require dealing with such events as additional intercurrent events. This would define additional estimands, possibly primary and secondary estimands all of which would deal with the COVID-19 related intercurrent events so that inference would still concern treatment effects in a world that is not in the midst of an extraordinary pandemic situation. The methodology for these estimands and additional sensitivity analyses for cases of missing data due to the impact of COVID-19 infections will be specified in detail in an amendment to the document developed in the event of renewed COVID-19 infection waves. Decisions on handling of possible increases in background risks impacting study endpoints will also take into consideration relevant epidemiological information on local incidence of COVID-19 infections.

2 Statistical methods

2.1 Data analysis general information

The final analysis will be performed by the sponsor. Data will be analyzed according to Section 12 of the CLNP023C12301 clinical study protocol. The most recent version of SAS and R® softwares available in the statistical programming environment will be used for the analysis. All analyses of data to be provided to the DMC will be carried out by an independent statistical group (CRO) as described in the DMC charter; the statistical analyses for the DMC will be drafted in a separate document.

2.1.1 General definitions

2.1.1.1 Study day

Study day is defined as the number of days since the date of first dose of study treatment. The date of first dose of study treatment is defined as Day 1 and the day before the first dose of study treatment is defined as Day -1.

Therefore, for a particular date, study day will be calculated as follows:

- for dates on or after the first date of study treatment,

  Study day = Assessment date – Date of first dose of study treatment + 1;

- for dates prior to the first date of study treatment,

  Study day = Assessment date – Date of first dose of study treatment.

If a patient never took study treatment, one day after the date of completion of screening assessments will be used instead of the date of first dose of study treatment. In that case, one day after the date of completion of screening assessments is defined as Day 1 and the day before the date of completion of screening assessments is defined as Day -1.

2.1.1.2 Baseline definition

For the analysis on efficacy and safety data in the core treatment period on the analysis sets FAS and SAF as defined in Section 2.2, the baseline value is defined to be the last result obtained at or prior to start of study treatment (Day 1) for baseline demographics, medical history, lab values, vital signs and ECGs. Most variables will have their baseline at Day 1, unless otherwise specified. For assessments not performed at Day 1, the assessment at the screening visit or most recent assessment prior to start of study treatment will be used as baseline. For baseline derivation of laboratory parameters, central lab measurements will be used. If there are no central lab data available, then local lab measurements will be used for baseline computations only.

- The baseline hemoglobin will be the mean of the two confirmatory measurements (planned) taken during screening that confirm the hemoglobin entry criterion in patients who do not receive a transfusion between the first and second confirmatory measurement. In patients who receive a transfusion after the first confirmatory measurement, the baseline will be the first measurement.

If there is only one confirmatory measurement but additional unplanned measurements taken during screening, for patients who do not receive transfusion in the screening, then the mean of the first measurement and the second measurement taken within 2 to 8 weeks after the first measurement will be considered to be the baseline. In patients who receive a transfusion after the first measurement, the baseline will be the first measurement. For patients with transfusion on same day, but hemoglobin measurement taken before transfusion, the baseline hemoglobin should be the average of the measurements considering the hemoglobin measurement before transfusion.

- The baseline score of fatigue using the FACIT-Fatigue questionnaire will be defined as the mean of first assessment prior to Day 1 and the Day 1 value. [redacted]
- The baseline LDH will be defined as the value on Day 1 (prior to starting treatment). If Day 1 value is not available, then the mean of two screening/LDH confirmatory values will be used. If screening value is not available, the baseline LDH will be defined as single confirmatory LDH value.

For the analysis on long term safety data on patients receiving iptacopan 200 mg b.i.d. in the core treatment period or the extension treatment period, the baseline value will be defined as the last result obtained prior to start of iptacopan 200 mg b.i.d.

2.1.1.3 Post baseline measurement

Post baseline measurements are defined as those assessments after the start of study treatment.

2.1.1.4 Change from baseline

When change from baseline is of interest the following formula will be used for each scheduled visit and time-point where baseline and post-baseline values are both available:

Change from baseline = post-baseline value – baseline value; and

If baseline or post-baseline values are missing, then the change from baseline will be missing.

2.1.1.5 Completion and last contact

A patient will complete the core treatment period when the patient has completed the Day 168 visit in the study or EOS for participants who discontinue from the study prior to the extension treatment period. The maximum of the date of last visit in the core treatment period, date of withdrawal of consent (in case of withdrawal from study), would be the date of last contact for the patient in the core treatment period.

2.2 Analysis sets

The **Screening set (SCR)** consists of all patients who have been screened. If a patient has been screened multiple times then the patient should be included for his/her last screening.

In Section 12.1 of Study protocol, the **Enrolled Set (ES)** comprises all participants enrolled in the study, which is equivalent to the **Screening set (SCR)**.

The **Full Analysis Set (FAS)** comprises all participants with confirmed eligibility to whom study treatment has been assigned. This will be the data set used for analysis of all efficacy endpoints.

The **Safety Set (SAF)** includes all participants who received at least one dose of study treatment.

2.3 Patient disposition, demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively for the FAS. In addition, summaries of relevant past or current medical conditions will be presented.

Categorical data will be presented as frequencies and percentages. The summary statistics shown for continuous data will be mean, standard deviation, median, minimum, and maximum.

2.3.1 Patient disposition

Core treatment period

The number of patients screened, screened but not treated, treated, completed and discontinued from the study in the core treatment period will be summarized. The reasons for screen failure will be provided. Participants discontinued from the study in the core treatment period will also be summarized with reasons for discontinuation. In addition, number of participants who discontinued study treatment, reason for discontinuation of study treatment and number of patients who discontinued study treatment but stayed in the core treatment period will be summarized. Participants who discontinued study treatment but continued in the study during the core treatment period are defined as participants with the date of study discontinuation or Day 168 visit - the end date of study treatment > 0.

Extension treatment period

The number of participants who completed and discontinued from the study in the Extension treatment period will be summarized. The reasons for discontinuation will be provided.

The number of subjects with protocol deviations, including those due to COVID-19, will be tabulated by deviation category and deviation for the FAS.

Based on FAS, the number of participants enrolled by country will be presented.

2.3.2 Relevant Medical History and current medical conditions

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology using the most recent version at the time when the last participant has completed the core treatment period. Medical history terms will be summarized by primary system organ class and preferred term. Hemoglobin history prior to screening (defined as mean result for hemoglobin obtained over a minimum of 6 months prior to screening), disease duration (as derived from the start date of PNH in Medical History page up to the date of screening) will be summarized separately.

History of MAVE (MAVEs prior to screening) will be summarized by medical history term. Transfusion history (the numbers of transfusions and unit numbers of packed-RBC received in the last 12 months prior to screening), transfusions up to 6 months prior to starting study treatment (yes, no) will be presented. [redacted] Vaccination history will be presented by serogroup/polyvalent.

Alcohol history will be reported based on usage (never, current, former). Smoking and vaping history will be presented based on type of substance (e-liquids, tobacco) and usage (never, current, former).

[redacted]

All the summaries will be presented on FAS.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatments

Treatment of interest

The investigational drug LNP023 (iptacopan) as 200 mg capsules, will be prepared by Novartis and supplied to investigator sites as open-label participant packs

Duration of treatment in the core treatment period

The duration of treatment iptacopan 200 mg b.i.d in the core treatment period is defined as the duration from the date of first administration of study treatment in the core treatment period to the date of last administration of iptacopan (any dose) in the core treatment period.

The end of the core treatment period is the date of last administration (any dose) in the core treatment period.

Duration of treatment in extension treatment period

The duration of iptacopan 200 mg b.i.d treatment in extension treatment period will be defined as the duration from the first date of administration of iptacopan 200 mg b.i.d in the day after Day 168 or the first administration of iptacopan 200 mg b.i.d in the extension treatment period to the date of last administration of iptacopan 200 mg b.i.d in the extension treatment period.

Overall duration of treatment

An overall duration of iptacopan 200 mg b.i.d treatment would include both core treatment period and extension treatment periods, with a start date and a stop date as described above for core treatment period and extension treatment periods, respectively.

Exposure and Dose Intensity for iptacopan

The Safety set (SAF) will be used for the analyses of exposure to iptacopan described below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure (in days) to iptacopan as well as the dose intensity and the relative dose intensity of iptacopan 200 mg b.i.d will be summarized by means of descriptive statistics using SAF during the core treatment period and for overall.

Duration of exposure to study treatment will be calculated as the number of days between the first dose date and the last dose date exposed to Iptacopan 200 mg b.i.d over the specified period but excluding temporary treatment interruptions (expressed as: Duration of exposure = Date of last known dose of study drug – Date of first dose of study drug + 1 excluding interruptions).

The duration of exposure to study treatment will be computed and summarized as the duration of treatment, but excluding temporary treatment interruptions. To establish the start of an interruption, the same rules should apply as for end of the duration of treatment described above.

An interruption will be defined as at least one full day without any dose.

Cumulative duration exposure on iptacopan 200 mg b.i.d based on SAF will be summarized as a categorical variable classified into ≤4, ≤8, ≤12, ≤16, ≤20, ≤24, ≤28, ≤32, ≤36, ≤40, ≤44, ≤48 weeks.

The duration of exposure will be the basis for the computation of the dose intensity and the relative dose intensity. The dose intensity for patients on iptacopan 200 mg bid will be computed as the ratio of actual cumulative dose received and actual duration of exposure. Relative dose intensity for patients on iptacopan 200 mg b.i.d will be computed as the ratio of dose intensity

and planned dose intensity. The planned dose intensity for patients on iptacopan 200 mg bid will be 400 mg/day. The dose intensity for patients on iptacopan will be summarized as a categorical variable classified into the categories stated in Table 2-1. Relative dose intensity will also be summarized on a continuous scale as well as considering categories (%): ≤ 75, > 75, > 90-100 and summaries on dose intensities will be presented on SAF.

The information on iptacopan +transfusions will be summarized as a categorical variable considering the dose intensity and tranfusions in the core treatment period. Summaries on the categories stated in Table 2-1. Such summaries will be presented on SAF.

For participants on iptacopan, the calculation of duration of treatment, exposure, dose intensity and relative dose intensity will include the investigational treatment iptacopan 200 mg b.i.d as well as the iptacopan tapering doses (if applicable).

Table 2-1 Summary on dose intensity and transfusions for patients on iptacopan

Dose intensity	Dose intensity and transfusions
<400 mg/day	<400 mg/day + no transfusion
400 mg/day	<400 mg/day + 1 transfusion
	<400 mg/day + ≥2 transfusions
	400 mg/day + no transfusion
	400 mg/day + 1 transfusion
	400 mg/day + ≥2 transfusions

For participants on iptacopan, an interruption will be defined as at least one full day without any dose. The number of participants with interruptions, number of interruptions and durations of interruptions will be summarized on SAF. The information on study medication intake for participants having at least one interruption will be listed. The number of participants with missed doses and number of missed doses will be summarized on SAF.

2.4.2 Prior, concomitant and post therapies

Medications and significant non-drug therapies started and stopped prior to study treatment, and those taken concomitantly, will be summarized based on SAF. Among the concomitant medications, rescue medications will be summarized based on SAF. The medications and significant non-drug therapies will be classified into “prior”, “concomitant”, “post-treatment” based on the start/end dates. The rescue therapy will be used for analysis as it is reported by the investigator under the subcategory of Rescue Medications/Therapy on the Concomitant Medication, Surgical and Medical Procedures CRF pages.Prior: Any medication and significant non-drug therapy with a start date and end date before Day 1.

Concomitant: Any medication or significant non-drug therapy administered at least once during the duration of the treatment (as defined in Section 2.4.1). It does not include 7 days after the last dose of iptacopan as in the definition of the on-treatment period for treatment emergent adverse event (TEAE). Medications started prior to first day of study drug intake and continuing after study drug start will be counted as concomitant.

Post-treatment medications will be defined as any medication with start date after the end of treatment (any dose).

A therapy started within 7 days after the last dose of iptacopan is not considered as concomitant although some TEAEs leading to concomitant medications may be reported in that period. The objective of this convention is to avoid reporting as concomitant medication some post treatment therapies targeting the study indication.

Prior, concomitant, post-treatment medications will be summarized according to the Anatomical Therapeutic Chemical (ATC) classification system. More than one ATC class per medication is possible and the medication will be reported under all applicable classes.

Prior, concomitant, post-treatment therapies will be recorded and summarized separately for surgical and medical procedures.

All vaccinations received by patients any time during the study (including core treatment period, extension treatment period) will be tabulated by serogroup/polyvalent and for each period. All vaccinations will also be recorded as prior and/or concomitant medication, as appropriate.

2.5 Analysis of the primary objective

For all efficacy analyses based on laboratory data (e.g. hemoglobin, reticulocytes etc.) addressing primary and secondary objectives, the information obtained from the central lab will be used.

2.5.1 Primary endpoint(s)/Primary estimand(s)

The primary endpoint defines the response as sustained increase in hemoglobin and a participant as a responder if :

- The change from baseline in hemoglobin is ≥ 2 g/dL on three out of four measurements taken at the visits occurring in last six weeks (from Day 126 to Day 168) of the Core treatment period, and
- The participant has not met the criteria for administration of RBC transfusions nor received a transfusion between Day 14 and Day 168.
- The baseline hemoglobin will be the mean of the two measurements taken during screening that confirm the hemoglobin entry criterion in patients who do not receive a transfusion between the first and second confirmatory measurement. In patients who receive a transfusion after the first confirmatory hemoglobin measurement, the baseline will be the first measurement.

Criteria for administration of RBC transfusions

To standardize criteria for administration, transfusion criteria have been established and will apply starting from Day 1 of the study.

Packed-RBC transfusions will be administered to participants in the following cases:

- Hemoglobin level of ≤9 g/dL (≤8 g/dL for Chinese population) with signs and/or symptoms of sufficient severity to warrant a transfusion
- Hemoglobin of ≤7 g/dL (≤6 g/dL for Chinese population), regardless of presence of clinical signs and/or symptoms

The transfusions information will be collected on the 'Transfusion-during the study' CRF page.

Handling of intercurrent events of primary estimand

Reaching the protocol established criteria for RBC transfusions will be handled using a composite strategy for primary endpoint.

Intercurrent events stemming from discontinuation of treatment, breakthrough hemolysis events and MAVEs, expected to be reflected in the endpoint, will be handled with a treatment policy strategy.

2.5.2 Statistical hypothesis, model, and method of analysis

2.5.2.1 Summary statistics for the primary variable

All descriptive statistics supportive of the primary variable will be based on non-imputed and observed data. For patients who did not require any RBC transfusion (i.e. not met the criteria for administration of RBC transfusions nor received a transfusion) between Day 14 and Day 168 separate summaries will be presented on the following information:

Number of patients having no-missing hemoglobin data in the in last six weeks (from Day 126 to Day 168), number of patients having an increase in hemoglobin ≥ 2 g/dL from baseline on three out of four measurements taken at the visits occurring in last six weeks (from Day 126 to Day 168) of the Core treatment period.

2.5.2.2 Statistical model for primary variable

The primary analysis of the primary endpoint will be a logistic regression to estimate the response probability. The covariates in logistic regression include 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) .

This means that the proportion of responders will be derived from the estimated marginal probabilities derived from the model fit as the mean of the individual logistic regression model predictions. The 95% confidence intervals will be derived by the bootstrap method (Steingrimsson et al 2017). Refer to Section 5.2.2.2 for details.

In the case that any of the 2^4 cells (given 4 covariates with 2 categories) have zero responders quasi-complete separation (Lu, 2016) may be observed. Moreover, in some imputed datasets or bootstrap samples, all participants are responders/non-responders, and this case will cause fit failure in logistic regression model.

Theoretically it can be shown that point estimate of the marginal probability from the logistic regression model and the simple response probability without the covariates are the same (Refer to Section 5.2.2.2). Since bootstrap is used to calculate the confidence interval, the confidence interval is also the same from the estimate from the logistic regression model and the simple proportion. Hence, the only reason why there can be a discrepancy in the results is due to a convergence issue (e.g. when all patients are responders/non-responders, quasi-complete separation issues due to covariates) of the logistic regression. However computation using simple proportion does not lead to such convergence issues and hence provide valid estimates.

The results from protocol specified logistic regression method and 95% CI using bootstrap will be computed. If the logistic regression fails to convergence in at least one of the imputed datasets or the bootstrap samples, then the estimates will be obtained using simple proportion. The 95% CI using simple proportion will also be obtained using the bootstrap method. Refer to Section 5.2.2.2 for details.

The primary analysis of primary endpoint is the assessment of the proportion of patients reaching the status of responder (as defined in Section 2.5.1). The lower bound of the two-sided 95% confidence interval of the response rate obtained from primary analysis will be compared to a threshold of 15%. Lower bound of the two-sided 95% confidence interval ≥ 15% is sufficient for demonstration that iptacopan improves hematological response in PNH patients with hemolysis and anemia in the absence of transfusions. The derivation of the threshold is explained in Section 5.2.2.3.

2.5.3 Handling of missing values not related to intercurrent event.

For the primary response definitions, RBC transfusion will qualify the participant as a non-responder, hence missing hemoglobin data after meeting the criteria for transfusion or after receiving a transfusion during Day 14 to Day 168 does not impact the primary analysis.

Missing hemoglobin data due to withdrawal from study in the core treatment period in the event that a participant did not have a prior RBC transfusion, will be imputed in a multiple imputation framework based on pattern mixture models. This aims to be consistent with the inclusion of hemoglobin data under the treatment policy strategy following all other intercurrent events. The need for transfusion will then be derived from this imputation with imputed values ≤ 9 g/dL (≤ 8 g/dL for Chinese population) considered sufficient to warrant a transfusion. This means assuming conservatively that all patients with imputed hemoglobin between 9 g/dL and 7 g/dL (between 8 g/dL and 6 g/dL for chinese patients) would have presented symptoms waranting transfusion.

- For participants withdrawing from study after discontinuation of iptacopan, the model implemented will recover a return to pre-treatment levels of Hb. This would be implemented by imputing missing values from a normal distribution with mean and standard deviation derived from all baseline hemoglobin values.
- For participants with intermittent missing data, their missing data will be handled with a missing at random approach and imputed consequently.

The model for imputation will be Markov chain Monte Carlo (MCMC) method and only baseline hemoglobin will be included in the imputation model.

2.5.4 Sensitivity analyses for primary endpoint/estimand

Sensitivity analyses on the primary endpoint will be performed where missing central lab hemoglobin data will be replaced by available local lab data collected at the same visit. The logistic regression model and simple proportion without any covariate adjustment which are used for primary efficacy analysis will be performed for these sensitivity analyses.

Additional sensitivity analyses on the primary analysis will be performed:

- Considering the need for transfusion derived from imputation with imputed values ≤ 7 g/dL (≤ 6 g/dL for Chinese population) to be sufficient to warrant a transfusion.

  This means assuming that none of the patients with imputed hemoglobin between 9 g/dL and 7 g/dL (between 8 g/dL and 6 g/dL for chinese patients) would have presented symptoms waranting transfusion.

- Considering administered transfusions.

2.5.5 Supplementary analyses

A supplementary estimand considering the use of rescue therapy (as defined in the study protocol) under intercurrent event as treatment failure, for the purpose of efficacy assessment, will be performed. The supplementary estimand will have the same population, treatment of interest, and summary measure as the primary estimand. The logistic regression model or simple proportion which is used for primary efficacy analysis will be performed for these supplementary analyses (see Section 2.5.2.2). For this analysis the following will be considered:

- Participant meeting the criteria for administration of RBC transfusions or having received a transfusion between Day 14 and Day 168 will be considered treatment failures.
- Use of rescue medication during the core treatment period between Day 1 and Day 168 will be considered treatment failures. The rescue therapy will be used for analysis as it is reported by the investigator under the subcategory of Rescue Medications/Therapy on the Concomitant Medication, Surgical and Medical Procedures CRF page.
- Discontinuations of study medication for any reason will be handled with treatment policy strategy.

The marginal proportions /response probabilities will be estimated using a logistic regression or simple proportion as for the primary variable (Section 5.2.2.2).

2.6 Analysis of secondary endpoints/estimands

2.6.1 Secondary endpoints/secondary estimands

Descriptive statistics and summaries on the secondary endpoints based on FAS will be provided.

2.6.1.1 Proportion of participants achieving sustained hemoglobin levels ≥ 12 g/dL in the absence of red blood cell transfusions

The number and percentage of patients reaching a fixed threshold ≥ 12 g/dL on three out of four measurements taken at the visits occurring in last six weeks (from Day 126 to Day 168).

The analysis of the secondary endpoint will be a logistic regression and simple proportion to estimate the response probability. The covariates in logistic regression include sex, age (indicator of age ≥ 45 years), an indicator variable of baseline hemoglobin ≥ 8 g/dL and an indicator of transfusion dependence prior to starting study treatment.

This means that the proportion of responders will be derived from the estimated marginal probabilities derived from the model fit as the mean of the individual logistic regression model predictions, together with the 95% confidence intervals, where the standard error will be derived by the bootstrap method (Steingrimsson et al 2017).

The marginal proportions /response probabilities will be estimated using a logistic regression or simple proportion as for the primary variable (Section 5.2.2.2).

2.6.1.2 Transfusion Avoidance

The number and percentage of patients not receiving and not meeting the criteria for administration of packed RBC tranfusions in the core treatment period will be summarized overall and by transfusion history during the last 6 months prior to starting study treatment (i.e. transfusion received/not received). The number and percentage of patients not receiving and not meeting the criteria for administration of any RBC transfusion between Day 14 and Day 168 will be summarized overall and by transfusion during the last 6 months prior to start of study treatment (i.e. transfusion received/not received). Time to first packed RBC transfusion from start of study treatment (Day 1) will be plotted using Kaplan Meier curves for overall and by transfusion during the last 6 months prior to start of study treatment (i.e. transfusion received/not received).

For RBC transfusions during the study, the hemoglobin level criterion deemed appropriate by the investigator for requiring the transfusion and signs and symptoms reported prior to receiving transfusion will be summarized. The information will be summarized based on the 'Transfusion-during the study' CRF page.

Transfusion avoidance will be evaluated as the proportion of participants not receiving and not meeting the criteria of administration of RBC transfusion between Day 14 and Day 168, and similarly to the estimation applied to the primary estimand (Section 2.5.2) by means of standardized marginal proportions. The logistic regression model will include sex, age (indicator of age ≥ 45 years), an indicator variable of baseline hemoglobin ≥ 8 g/dL and an indicator of transfusion dependence.

The marginal proportions /response probabilities will be estimated using a logistic regression or simple proportion as for the primary variable (Section 5.2.2.2).

2.6.1.3 Change from baseline in hemoglobin levels

Estimation of change from baseline in hemoglobin levels is under the hypothetical situation in which participants would not have received transfusions on iptacopan treatment. For this analysis, if a participant had a transfusion during the core treatment period then the hemoglobin values 30 days following the transfusion will be considered missing and hemoglobin data will be imputed. In practice, this would be implemented considering participants on iptacopan to have data imputed assuming missing at random. This will be accomplished by the use of imputed values (Section 2.5.3).

The model for the estimation is a mixed model for repeated measures (MMRM) considering an unstructured covariance structure. The model will include transfusion dependence, age (indicator of age ≥ 45 years), sex, visit, baseline hemoglobin and the interactions between visits and baseline levels. The treatment estimates will be 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 estimated least square mean estimate of the treatment effect and the associated 95% confidence interval will be plotted over time. Refer to Section 5.2.3 for detail.

2.6.1.4 Change from baseline in FACIT-Fatigue scores

The endpoint consists of changes from baseline in scores of fatigue using the FACIT-Fatigue questionnaire where baseline is defined as in Section 2.1.1.2. As for the other endpoints, the longitudinal model will be a repeated measures model including test scores collected at all visits.

The model for the estimation is a MMRM considering an unstructured covariance strucure. The model will include 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 will be an average of treatment estimates derived for visits occurring between Day 126 and Day 168. The estimated least square mean estimate of the treatment effect and the associated 95% CI will be plotted over time.

2.6.1.5 Change from baseline in reticulocyte counts

The estimation of the change from baseline in absolute reticulocyte counts will be derived from a MMRM including data collected throughout the study and where baseline is defined as the value on Day 1. The model for the estimation is a MMRM considering an unstructured covariance structure. The model will include transfusion dependence, age (indicator of age ≥ 45 years), sex, visit, baseline reticulocyte counts and the interactions between visits and baseline levels.

The estimation will use the average of model derived estimates obtained at visits occurring between Day 126 and Day 168. The estimated least square mean estimate of the treatment effect and the associated 95% CI will be plotted over time.

2.6.1.6 Percent change from baseline in LDH

The treatment effect on percent change from baseline in LDH will be assessed using a MMRM of log transformed ratio to baseline based on all observations collected during follow-up. The model for the estimation is a MMRM considering an unstructured covariance structure. The model will include 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 will be derived based on the average of the log transformed ratio from baseline estimated between Day 126 and Day 168. Percentage change from baseline (reduction or increase) and associated 95% confidence intervals will be plotted for treatment effect over time.

2.6.1.7 Rates of Major Adverse Vascular Events (MAVE)

Information of MAVEs as collected on the 'MAVE' CRF page will be used for analysis and the information will also be reported as a part of the adverse event summaries. The number and percentage of participants with treatment-emergent (MAVEs) in the core treatment and extension treament periods will be summarized by reported term. The information on MAVEs (including those in the screening period) will be listed and the treatment emergent events will be flagged.

Based on FAS, the estimation of rates of MAVEs will be carried out using a negative binomial model. Due to the expected low frequency of occurrences, no covariates are planned to be included. Following the treatment policy strategy for handling treatment discontinuations, the offset variable will be defined as the time from Day 1 till minimum (end of study, end of core treatment period).

If the model fails to converge, then a Poisson model without covariates will be fitted. If both negative binomial and Poisson model fail to converge, the Wilson (Miettinen and Nurminen, 1985) method will be implemented to produce 95% CI.

2.6.1.8 Rates of clinical breakthrough hemolysis

Information of clinical breakthrough events as collected on the 'Breakthrough Hemolysis' CRF page will be used for analysis and the information will also be reported as a part of the adverse event summaries. The number and percentage of patients experiencing treatment emergent clinical breakthrough hemolysis events in the core treatment and extension treatment periods will be summarized. The information on whether the patient received packed-RBC transfusions and the quantity of packed-RBC tranfusions due to clinical breakthrough hemolysis will be summarized. Clinical breakthrough hemolysis events (including those in the screening period) will be listed and the treatment emergent events will be flagged.

Based on FAS, the estimation of rates of clinical breakthrough hemolysis will be carried out using a negative binomial model . The model will include the following covariates: transfusion dependence, age (indicator of age ≥ 45 years), sex, indicator variable of baseline hemoglobin ≥ 8 g/dL. Following the treatment policy strategy for handling treatment discontinuations, the offset variable will be defined as the time from Day 1 till minimum (end of study, end of core treatment period).

If the above model fails to converge due to low frequency of occurrences, then the model will be run considering no covariates in the negative binomial model. If the model fails to converge, then a Poisson model without covariates will be fitted. If both negative binomial and Poisson model fail to converge, the Wilson (Miettinen and Nurminen, 1985) method will be implemented.

2.6.2 Handling of missing values for secondary endpoints

Missing data during study follow up will be imputed following the same principles as for the primary estimands/endpoints: intermittent missing data will be imputed according to the missing at random (MAR) principle. Missing data due to withdrawal from the study or discontinuation for iptacopan treatment will be imputed by recovering a return to pre-treatment levels. This would be implemented by imputing missing values from a normal distribution with mean and standard deviation derived from all baseline values. In case of intermittent missing data, their missing data will be handled with a missing at random approach and imputed consequently.

The model for imputation will be Markov chain Monte Carlo (MCMC) method, and only baseline values will be included in the imputation model.

For the transfusion avoidance endpoint the handling of missing data will be very similar to the handling of missing data for the primary endpoints and the same multiple imputed datasets can be used.

For the specific case of missing hemoglobin due to withdrawal, the imputation will reflect whether or not data were missing following a transfusion.

In the case of definitive withdrawal of study follow up following a transfusion only hemoglobin levels at visits during 30 days following the transfusion and until treatment discontinuation would be imputed under the MAR assumption. The missing hemoglobin after treatment discontinuation will be imputed by recovering a return to pre-treatment levels of hemoglobin. This would be implemented by imputing missing values from a normal distribution with mean and standard deviation derived from all baseline values. More specifically a patient should be first imputed in the hypothetical scenario for hemoglobin until end of treatment. In case of definite withdrawal of study follow up without transfusion missing data will be imputed as stated in Section 2.5.3.

In all estimation based on a longitudinal model, missing data will be imputed multiple times. The imputed datasets will be used in the estimation of the longitudinal model. Where both intercurrent events (as for the hypothetical estimand estimating hemoglobin levels) and missing data are imputed or where only missing data are imputed, the model estimation will be derived using Rubin's combination rules.

For endpoints, eg. FACIT-fatigue which are constrained to be in a finite range of values, if some imputed values are lower than the limit, then they will be truncated to the lower limit and if some imputed values exceed the upper limit then they will be truncated to the upper limit.

2.6.3 Sensitivity analyses

Sensitivity analyses will be performed where missing central lab data will be replaced by available local lab data collected at the same visit. MMRM for analysis of change from baseline in hemoglobin under a hypothetical strategy, change from baseline in reticulocytes, and change from baseline in LDH levels stated in Section 2.6.1.1, 2.6.1.2, 2.6.1.3, 2.6.1.5, 2.6.1.6, respectively, will be performed.

Additional sensitivity analyses will be performed for hemoglobin normalization (Section 2.6.1.1) and transfusion avoidance (Section 2.6.1.2):

- Considering the need for transfusion derived from imputation with imputed values ≤ 7 g/dL (≤ 6 g/dL for Chinese population) to be sufficient to warrant a transfusion.
- Considering administered transfusions.

2.6.4 Supportive analyses

To complement the secondary estimand analysis of average changes in hemoglobin under a hypothetical strategy, the analysis evaluating average changes in hemoglobin will be repeated using a treatment policy approach, to obtain the estimation of the combination of Iptacopan+transfusions as needed.

Supportive analyses on the secondary endpoints: change from baseline in LDH, FACIT, reticulocytes will be performed under a hypothetical strategy. For these analyses, the values on these 3 endpoints in the 30 days following transfusion will be considered missing and the values will be imputed. The imputation methods will be similar to those outlined in Section 2.6.2.

2.7 Safety analyses

Unless otherwise specified all safety summaries will be presented by SAF. Safety summaries based on only core treatment period and overall (based on information from core treatment period and extension treatment period) will be produced as appropriate.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g., change from baseline summaries). In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs). In addition, a separate summary of death events including on treatment and post treatment deaths will be provided if appropriate.

The on-treatment period lasts from the date of first administration of study treatment to 7 days after the date of the last actual administration (including core treatment period, extension treatment period and tapering procedures after permanent treatment discontinuation) of iptacopan which covers slightly more than 5 times the estimated half-life of iptacopan.

2.7.1 Adverse events (AEs)

All information obtained on AEs will be displayed by participant.

The number (and percentage) of participants with treatment emergent AEs (events starting after the first dose of study medication or events present prior to start of treatment but increased in

severity based on preferred term) and treatment emergent serious adverse events (SAEs) will be summarized in the following ways:

- by primary system organ class (SOC) and preferred term (PT).
- by primary SOC, PT and maximum severity.

Separate summaries will be provided for study treatment emergent AEs, death, SAEs, and AEs leading to discontinuation of study medication, and for iptacopan tapering if this is followed prior to complete study dose discontinuation. For patients receiving iptacopan, treatment emergent SAEs and AEs with PTs in the AESI 'PNH haemolysis and thrombosis' occurring after dicontinuation of iptacopan 200 mg b.i.d will be reported separately.

A participant with multiple AEs within a primary SOC is only counted once towards the total of the primary SOC.

Most frequent AEs, most frequent SAEs, AEs leading to treatment discontinuation will be presented by preferred term.

Summaries presenting exposure adjusted incidence rates and associated 95% CI based on TEAEs and treatment emergent SAEs will be provided. AEs (including pre-treatment, on-treatment, post-treatment events) will be listed.

In order to address the issue of variable follow-up duration within study, the exposure adjusted incidence rate of TEAE will be presented by primary SOC and PT.

For the most common AEs, the 95% CI of the exposure adjusted incidence rate of TEAE can be presented.

Exposure adjusted incidence rate and 95% confidence interval

For summary tables on exposure-adjusted AEs, the number of episodes per 100 patient years will be presented. The occurrence rate (number of episodes per 100 patient years) will be calculated as 100*(the total number of AE episodes from all patients in the population divided by the total number of patient-years). A patient may have multiple occurrences of the same event. All occurrences are counted. Total patient years will be computed as (sum of the duration of on-treatment periods over patients, in days)/365.25. The approximately 95% CIs for the occurrence rate will be calculated with correation for overdispersion using the asymptotically robust method (Scosyrev 2016, Scosyrev and Pethe 2022).

This method will account for the length of follow-up time under the assumption that events would occur with the same frequency at any point in time. Although this analysis is referred to as "Exposure adjusted" it actually uses by default the on-treatment (Section 2.7) which includes periods of interruption during which there is no exposure.

2.7.1.1 Adverse events of special interest / grouping of AEs

Adverse events of special interest (AESI) are defined in the latest version of the compound electronic Case Retrieval Strategy (eCRS) that is stored in the Global Programing System (GPS). This classification reflects the safety topics of interest identified in the current version of the iptacopan Development Safety Profiling Plan, and may be updated based on review of accumulating data. At the time of analyses, the latest version of the eCRS will be used to identify the AESIs. Safety topics of interest to be reported are identified by the flag "SP".

The number (and percentage) of participants with treatment-emergent adverse events of special interest/related to identified and potential risks will be summarized. The frequency and percentage of participants with treatment emergent adverse events of special interest (TEAESI) and serious TEAESI will be summarized by preferred team. The exposure adjusted incidence rates and associated 95% CI (as stated in Section 2.7.1) will be presented for each safety topic of interest AEs/SAEs.

A listing of participants experiencing AESIs will also be provided. The eCRS safety topic definitions to identify AESIs will be provided as a listing.

For patients receiving iptacopan, treatment-emergent and all AESI within the search 'PNH haemolysis and thrombosis' occurring after discontinuation of iptacopan 200 mg b.i.d will be reported. All such AEs occuring after iptacopan 200 mg b.i.d will be listed and the TEAEs will be flagged.

2.7.1.2 Adverse events reporting for safety disclosure

For the legal requirements of clinicaltrials.gov and EudraCT, two required tables on TEAEs which are not SAEs with an incidence greater than a certain threshold and on TESAEs and SAE suspected to be related to study treatment, will be provided by SOC and PT on the safety set population. If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.7.2 Deaths

The number of deaths resulting from TEAEs will be summarized by SOC and PT. Death refers to TEAEs with fatal outcome. In addition, a separate summary of death events including on treatment and post treatment deaths will be provided if appropriate.

All the deaths in the clinical database will be listed.

2.7.3 Laboratory data

For all safety analysis based on laboratory data, the information obtained from the central as well as local labs will be used. For summaries by visits, local lab data will be used when the corresponding central lab data are missing. For summaries on overall post-baseline data, all available data (including central and local lab data) from scheduled and unscheduled visits will be used.

Laboratory evaluations' summaries will be presented for groups of laboratory data (clinical chemistry, clinical hematology, urinalysis, UACR, coagulation/markers of thrombosis and reproductive and thyroid hormone panel).

For all continuous laboratory parameters, the absolute on-treatment laboratory values will be summarized with standard descriptive statistics (mean, median, standard deviation, minimum, maximum) by parameter, and scheduled visit/time-point. The on-treatment laboratory values will be defined as in Section 2.7.

For categorical laboratory parameters and categorical urinalysis parameters, a frequency table of results will be produced by laboratory parameter, scheduled visit and time-point.

It is to be noted that for analysis on SAF, different baseline values need to be considered as mentioned in Section 2.1.1.2.

For summary tables on laboratory parameters considering values, which are lower or greater than the limit of quantification:

- The values less than Lower Limit of Quantification (LLoQ) will be imputed to 0.5×LLoQ and the values greater than Upper Limit of Quantification (ULoQ) will be imputed to 1.5×ULoQ.
- The number and percentage of values below the LLoQ and above the ULoQ will be presented.

For the figures, imputed values will be displayed.

Plots of arithemic mean (SD) for all lab values will be provided. Note that displays of reproductive hormone level parameters (Testosterone, DHT, LH, FSH) will be further split by sex.

The lab abnormalities using the CTCAE grading will be reported. The version 4.03 of the CTCAE grading will be used at the time of reporting and the following reports will be provided:

- New or worsening abnormalities based on CTCAE grade (hematology, chemistry)
- Shift tables based on CTCAE grade (hematology, chemistry).

For selected laboratory parameters, abnormalities occurring at any time-point from scheduled, unscheduled and premature discontinuation visits considering all post-baseline on-treatment data will be summarized. Where normal ranges are available, abnormalities in laboratory data will be listed by participant and visit/time.

Liver toxicities

A criterion-based table for selected liver function tests and AEs will be presented including the number and percentage of the events described in Table 2-2. In the PNH indication, aspartate aminotransferase (AST) can increase for reasons not related to liver toxicity and therefore should not be considered in the derivation of liver toxicities. Moreover INR is routinely monitored and can be used for the definition of liver function events. Events for the PNH indication are described in Table 2-2.

Liver toxicity finding based on laboratory values and accounting for presence of bone pathology, symptoms, Gilbert syndrome will be presented. AEs collected in the analysis dataset and related

to liver toxicities (Jaundice, AE potentially indicative of a liver toxicity) will either be reported separately in a specific table or will simply be displayed as part of the general AE tables.

Table 2-2 Liver Toxicities

Definition	Label for output display
Potential Hy's Law case	
(ALT or AST > 3 × ULN) and TBL > 2 × ULN and ALP to ≤ 2 × ULN in the absence of bone pathology[a] (ALT or AST > 3 × ULN) and TBL > 2 × ULN and ALP to ≤ 3 × ULN in the presence of bone pathology[a]	Potential Hy's Law case
ALT elevations	
If ALT ≤ ULN at baseline: (ALT > 3 × ULN) and INR > 1.5 If ALT > ULN at baseline then criteria for ALT are defined as ALT > 2 x baseline or > 300 U/L and INR > 1.5	(ALT > 3 × ULN) and INR > 1.5
ALT > 8 × ULN	ALT > 8 × ULN
If ALT ≤ ULN at baseline: ALT > 5 to ≤ 8 × ULN If ALT > ULN at baseline then criteria for ALT are defined as ALT > 3 x baseline or > 300 U/L	ALT > 5 to ≤ 8 × ULN
If ALT ≤ ULN at baseline: ALT > 3 to ≤ 5 × ULN (accompanied by symptoms)[a] If ALT > ULN at baseline then criteria for ALT are defined as ALT > 2 x baseline or > 300 U/L (accompanied by symptoms)[a]	ALT > 3 to ≤ 5 × ULN with symptoms
If ALT ≤ ULN at baseline: ALT > 3 to ≤ 5 × ULN (patient is asymptomatic)[a] If ALT > ULN at baseline then criteria for ALT are defined as ALT > 2 x baseline or > 300 U/L (patient is asymptomatic)[a]	ALT > 3 to ≤ 5 × ULN no symptoms
ALP (isolated)	
ALP > 2 × ULN (in the absence of known bone pathology)[a] ALP >3 x ULN (if bone pathology[a] is present)	ALP > 2 × ULN (>3 x ULN if bone pathology is present)
TBL: total bilirubin ALT: alanine aminotransferase [a] concomitance between abnormal laboratory values and symptoms or disease (bone disease, Gilbert syndrome) will be established based on reported AEs or medical history with a start date prior to laboratory measurement and stop date posterior to laboratory measurement. Selection of AEs and medical History is described in Table 2-3 and provided in eCRS [b] Selection of AEs described in Table 2-3 and provided in eCRS	

When a criterion contains multiple laboratory parameters (e.g. ALT or AST > 3 × ULN), the criterion should considered as met only if the elevation in parameters occurs on the same sample day (as evidenced by the same date that the lab samples were taken).

Table 2-3 Definition of symptoms and AEs for liver toxicities

Term in table	MedDRA term(s)
Bone pathology	HLGT = Bone disorders (excl congenital and fractures)
Symptoms:	
Severe Fatigue (1)	PT = Fatigue
Abdominal pain right upper quadrant	PT = Abdominal pain upper
Nausea	PT = Nausea
Vomiting	PT = Vomiting
General malaise	PT = Malaise
Rash with eosinophilia	PT = Drug reaction with eosinophilia and systemic symptoms
Gilbert syndrome	PT = Gilbert's syndrome
Jaundice	PT = Jaundice PT = Jaundice cholestatic
AEs indicative of liver toxicity	
Hepatic failure	HLT = Hepatic failure and associated disorders
Hepatic fibrosis and cirrhosis	HLT = Hepatic fibrosis and cirrhosis PT = Hepatic cirrhosis
Non-infectious hepatitis	PT = Hepatitis PT = Hepatitis acute PT = Hepatitis toxic PT = Hepatitis fulminant PT = Hepatitis chronic active PT = Hepatitis chronic persistent
Liver neoplasm	HLGT = Hepatobiliary neoplasms

HLT: High Level Term
HLGT: High Level Group Term
MedDRA codes listed above are based on version 23.1 The list will be updated for each MedDRA version change and will be included in the eCRS. eCRS will be the reference for analyses.
(1) presence of Fatigue term with severity ≥ "Severe"

Renal alert values will be summarized where renal alert values are identified as:

- Serum creatinine increase ≥ 25% compared to baseline during normal hydration status
- New onset dipstick proteinuria ≥ 3+

2.7.3.1 Electrocardiogram (ECG)

The following ECG parameters will be obtained during the study and summarized descriptively: ECG mean heart rate, RR interval, PR interval, QRS duration, QT interval and corrected QT interval by the Fridericia criteria (QTcF). Summary statistics (absolute values and change from baseline) for all ECG parameters will be provided by time point; the number of participants with values outside the normal range will be displayed. Where normal ranges are available, participants with abnormalities in ECG data will be listed by visit/time.

Categorical summary statistics for ECG alert values will also be provided based on the number and proportion of participants meeting or exceeding the following predefined limits any time post baseline:

- QRS > 120 ms
- QRS increase from baseline > 25%
- QTcF > 500 ms
- QTcF increase from baseline > 60 ms
- Resting heart rate sinus rhythm (HR) < 30 bpm
- HR decrease from baseline ≥ 25%
- HR > 130 bpm

In addition, a listing of these participants will be produced. A listing of all newly occurring or worsening abnormalities will be provided.

Noticeable ECG abnormalities such as ventricular tachychardia, new complete heart block (Grade III AV block) and Mobitz II AV block are reported as AEs and will be described as part of AEs.

When ECG is performed in triplicate at each visit, the average between the 3 values must be used for summaries and before identification of the abnormalities listed above.

2.7.3.2 Vital signs

Vital signs measurements include systolic blood pressure (SBP) and diastolic blood pressure (DBP), pulse rate, body temperature, height and body weight. Summary statistics (absolute on-treatment values and change from baseline) will be provided for all vital signs data (weight, temperature, pulse rate, SBP, DBP) by visit/time. On-treatment values will be defined as in Section 2.7.

Where ranges are available, abnormalities will be summarized and listed by participant and visit/time. Arithmetic mean (SD) of absolute values over time for SBP , DBP and pulse rate will also be provided.

Frequency tables displaying the number of patients with abnormal blood pressure or heart rate values (by visit or worst post baseline) can be displayed.

Boundaries are the following:

- Blood pressure (BP):
    1. Systolic BP: 100 – 140 mmHg

2. Diastolic BP: 65 – 95 mmHg

- Heart rate:
    1. <=50 bpm
    2. >=120 bpm
- Temperature > 38.3 °C (>101 °F)

[redacted]

2.10 Patient-reported outcomes

In this study, the question addressed by the analysis of PRO measurements is whether treatment with iptacopan improves patient-reported fatigue symptoms as measured by the FACIT-Fatigue.

[redacted]

[redacted]

Changes in scores of fatigue using the FACIT-Fatigue questionnaire are a secondary endpoint and the analysis is described in Section 2.6.

[redacted]

All supportive analyses of the performance of the FACIT-Fatigue questionnaire (including responder analyses derived from a priori definition of a meaningful change) and of the behavior of meaningful change over time as well as of the impact of clinical endpoints as reflected in the FACIT-Fatigue will be detailed in a separate analysis plan for PROs.

[redacted]

[redacted]

2.13 Interim analysis

No formal interim analyses of efficacy are planned in this study. A data cut-off will be applied and a clinical study report (CSR) will be produced for submission at the time the last patient has completed the core treatment period. An additional CSR will be produced when the last participant has completed the last visit in the extension treatment period, when the final study database has been locked. In addition, if deemed required (e.g. to support regulatory submissions to Health Authorities) interim safety analyses may be produced while the study is still ongoing. If there is an interim lock for safety analyses, [redacted] The interim report will not consider inferences based on efficacy.

Safety data will be monitored by an independent DMC, and analyses to the effect of this evaluation will be performed during the course of the study with the frequency to be determined in the DMC Charter. Access to a limited number of efficacy measurements by the DMC will be

provided solely for the purpose of evaluating benefit of treatment with iptacopan against any risk. The DMC will function under the the DMC Charter which has been finalized. The Charter includes guidelines for communication concerning safety of participants between the DMC and the sponsor representative to ensure that these are in keeping with the sensitive nature of the open label trial and do not introduce bias.

3 Sample size calculation

The sample size is calculated based on the half-width (the margin of error in the estimate) of a 2-sided 95% confidence interval for the proportion of participants reaching the status of responder (primary endpoint). The proposed sample size of 40 participants is sufficient to achieve a target absolute margin of error not larger than 0.155.

The different scenarios of observed response rate and its 95% confidence intervals are shown in Table 3-1.

Table 3-1 Precision of response rate with N = 40

Sample Size	Observed Response Rate	Unadjusted 95% Confidence Interval
40	30%	(15.8%,44.2%)
40	40%	(24.8%,55.2%)
40	50%	(34.5%, 65.5%)
40	60%	(44.8%,75.2%)

The lower bound of the two-sided 95% confidence interval of the response rate obtained from the primary analysis will be compared to a threshold of 15% and exceeding the threshold is sufficient for demonstration that iptacopan improves hematological response in PNH patients with hemolysis and anemia in the absence of transfusions.

For the sample size of 40 participants, given the observed proportion of responders is 40%, there is 96.4% probability that the lower bound of the 2-sided 95% CI will exclude a threshold of 15%.

4 Change to protocol specified analyses

The “indicator of transfusion dependence” is defined to be “prior to starting study treatment” instead of “at enrollment” (defined in study protocol Section 12.4.2).

5 Appendix

5.1 Imputation rules

5.1.1 AE date imputation

5.1.1.1 AE end date imputation

Rules for imputing AE end dates are stated below. Date of last contact in the study has been defined as in Section 2.1.1.5 .

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the (date of last contact, 31DECYYYY, date of death).
2. If the AE end date day is missing, the imputed end date should be set to the earliest of the (date of last contact, last day of the month, date of death).
3. If AE year is missing or AE is ongoing, the end date will not be imputed.

5.1.1.2 AE start date imputation

Rules for imputing the AE start date:

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial Adverse Event Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) No convention	(1) No convention	(1) No convention	(1) No convention
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.c) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

Before imputing AE start date, find the AE start reference date.

1. If the imputed AE end date is complete and the imputed AE end date < treatment start date then AE start reference date = min(informed consent date, earliest visit date).
2. Else AE start reference date = treatment start date

Impute AE start date -

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:

a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).

b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).

3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:

   a. If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).

   b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

4. If the AE start date year value is equal to the treatment start date year value:

   a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.

   b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).

   c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete imputed AE end date is available and the imputed AE start date is greater than the imputed AE end date, then imputed AE start date should be set to the imputed AE end date.

5.1.2 Concomitant medication date imputation

5.1.2.1 Concomitant medication end date imputation

Rules for imputing the CM end date are stated below. Date of last contact in the study has been defined as in Section 2.1.1.5. Concomitant medication end dates will not be imputed for ongoing records.

1. If CM end day is missing and CM month/year are non-missing then impute CM day as the minimum of date of last contact and the last day of the month.
2. If CM end day/month are missing and CM year is non-missing then impute CM day as the minimum of date of last contact and the end of the year (31DECYYYY).
3. If CM day/month/year is missing then use the date of last contact + 1 day as the imputed CM end date.
4. If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.

5.1.2.2 Concomitant medication start date imputation

Rules for imputing the CM start date:

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial CMD Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) Uncertain	(1) Uncertain	(1) Uncertain	(1) Uncertain
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.a) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.
2. If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the mid-year point (01JulYYYY).
    b. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).
3. If the CM start date year value is greater than the treatment start date year value, the CM started after treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the year start point (01JanYYYY).
    b. Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).
4. If the CM start date year value is equal to the treatment start date year value:
    a. And the CM month is missing or the CM month is equal to the treatment start date month, then the imputed CM start date is set to one day prior treatment start date.
    b. Else if the CM month is less than the treatment start date month, the imputed CM start date is set to the mid-month point (15MONYYYY).
    c. Else if the CM month is greater than the treatment start date month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete imputed CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

5.2 Statistical models

5.2.1 Tabular view of estimands and associated estimation methods

Table 5-1 Overview of estimands and estimation methods

Estimand	Endpoint	Handling strategy of intercurrent events				Summary measure
		Discontinuation of study medication	Breakthrough hemolysis events	MAVEs	RBC transfusions	
Primary estimands						
Primary estimand	composite of: increase in Hb levels ≥ 2 g/dL from baseline* without requiring RBC transfusions[#]	Treatment policy Missing data on iptacopan after study discontinuation imputed using "returen to pre-treatment"	Treatment policy	Treatment policy	Not an intercurrent event- included in the composite estimand	Proportion of responders
Sensitivity analysis (Primary)1	composite of: increase in Hb levels ≥ 2 g/dL from baseline* without requiring RBC transfusions[#]	Treatment policy Missing hemoglobin central lab data replaced by local lab data at same visit. Missing data on iptacopan after study discontinuation imputed using "return to pre-treatment"	Treatment policy	Treatment policy	Not an intercurrent event- included in the composite estimand	Proportion of responders
Sensitivity analysis (Primary) 2	composite of: increase in Hb levels ≥ 2 g/dL from baseline* without requiring RBC transfusions[#]	Treatment policy Missing data on iptacopan after study discontinuation imputed using "returen to pre-treatment" Considering the need for transfusion derived from imputation with imputed values ≤ 7 g/dL (≤ 6 g/dL for Chinese	Treatment policy	Treatment policy	Not an intercurrent event- included in the composite estimand	Proportion of responders

Estimand	Endpoint	Handling strategy of intercurrent events				Summary measure
		population) to be sufficient to warrant a transfusion.				
Sensitivity analysis (Primary) 3	composite of: increase in Hb levels ≥ 2 g/dL from baseline* without requiring RBC transfusions[#]	Treatment policy Missing data on iptacopan after study discontinuation imputed using "returen to pre-treatment" Considering administered imputation	Treatment policy	Treatment policy	Not an intercurrent event- included in the composite estimand	Proportion of responders
Supplementary estimands						
Supplementary estimand	composite of: increase in Hb levels ≥ 2 g/dL from baseline* without requiring RBC transfusions[#] and not receiving rescue medication[$f]	Treatment policy Missing data on iptacopan after study discontinuation imputed using "return to pre-treatment"	Treatment policy	Treatment policy	Not an intercurrent event- included in the composite estimand	Proportion of responders
Secondary estimands						
Secondary estimand 1	composite of: having Hb levels ≥ 12 g/dL* without requiring RBC transfusions [#]	Treatment policy Missing data on iptacopan after study discontinuation imputed using "return to pre-treatment"	Treatment policy	Treatment policy	Not an intercurrent event- included in the composite estimand	Proportion of responders
Sensitivity analysis (Secondary) 1.1	composite of: having Hb levels ≥ 12 g/dL* without requiring RBC transfusions [#]	Treatment policy Missing hemoglobin central lab data replaced by local lab data at same visit. Missing data on iptacopan after study discontinuation imputed using "return to pre-treatment"	Treatment policy	Treatment policy	Not an intercurrent event- included in the composite estimand	Proportion of responders

Estimand	Endpoint	Handling strategy of intercurrent events				Summary measure
Sensitivity analysis (Secondary) 1.2	composite of: having Hb levels ≥ 12 g/dL* without requiring RBC transfusions [#]	Treatment policy Missing data on iptacopan after study discontinuation imputed using "returen to pre-treatment" Considering the need for transfusion derived from imputation with imputed values ≤ 7 g/dL (≤ 6 g/dL for Chinese population) to be sufficient to warrant a transfusion.	Treatment policy	Treatment policy	Not an intercurrent event- included in the composite estimand	Proportion of responders
Sensitivity analysis (Secondary) 1.3	composite of: having Hb levels ≥ 12 g/dL* without requiring RBC transfusions [#]	Treatment policy Missing data on iptacopan after study discontinuation imputed using "returen to pre-treatment" Considering administered imputation	Treatment policy	Treatment policy	Not an intercurrent event- included in the composite estimand	Proportion of responders
Secondary estimand 2	Proportions of participants not receiving any transfusions [#]	Treatment policy Missing data on iptacopan after study discontinuation imputed using "return to pre-treatment"	Treatment policy	Treatment policy	Not an intercurrent event since this is the endpoint of interest	Proportion of responders
Sensitivity analysis 2.1	Proportions of participants not receiving any transfusions [#]	Treatment policy Missing hemoglobin central lab data replaced by local lab data at same visit.	Treatment policy	Treatment policy	Not an intercurrent event- included in the composite estimand	Proportion of responders

Estimand	Endpoint	Handling strategy of intercurrent events				Summary measure
		Missing data on iptacopan after study discontinuation imputed using "return to pre-treatment"				
Sensitivity analysis (Secondary) 2.2	Proportions of participants not receiving any transfusions [#]	Treatment policy Missing data on iptacopan after study discontinuation imputed using "returen to pre-treatment" Considering the need for transfusion derived from imputation with imputed values ≤ 7 g/dL (≤ 6 g/dL for Chinese population) to be sufficient to warrant a transfusion.	Treatment policy	Treatment policy	Not an intercurrent event- included in the composite estimand	Proportion of responders
Sensitivity analysis (Secondary) 2.3	Proportions of participants not receiving any transfusions [#]	Treatment policy Missing data on iptacopan after study discontinuation imputed using "returen to pre-treatment" Considering administered imputation	Treatment policy	Treatment policy	Not an intercurrent event- included in the composite estimand	Proportion of responders
Secondary estimand 3	Hemoglobin changes from baseline**	Treatment policy Missing data on iptacopan after study discontinuation imputed using "return to pre-treatment"	Treatment policy	Treatment policy	Transfusions[#] are treated within a hypothetical strategy (as if patients had not received any transfusions)	Mean change from baseline in hemoglobin levels
Sensitivity analysis (Secondary) 3.1	Hemoglobin changes from baseline**	Treatment policy	Treatment policy	Treatment policy	Same	Mean change from baseline in hemoglobin levels

Estimand	Endpoint	Handling strategy of intercurrent events				Summary measure
		Missing hemoglobin central lab data replaced by local lab data at same visit. Missing data on iptacopan after study discontinuation imputed using "return to pre-treatment"				
Supportive analysis (Secondary) 3.1	Hemoglobin changes from baseline**	Treatment policy Missing data on iptacopan after study discontinuation imputed using "return to pre-treatment"	Treatment policy	Treatment policy	Treatment policy	Mean change from baseline in hemoglobin levels
Secondary estimand 4	Change from baseline in scores of fatigue using the FACIT Fatigue questionnaire**	Treatment policy Missing data on iptacopan after study discontinuation imputed using "return to pre-treatment"	Treatment policy	Treatment policy	Treatment policy	Mean change from baseline in FACIT fatigue scores
Supportive analysis (Secondary) 4.1	Change from baseline in scores of fatigue using the FACIT Fatigue questionnaire**	Treatment policy Missing data on iptacopan after study discontinuation imputed using "return to pre-treatment"	Treatment policy	Treatment policy	Hypothetical Policy	Mean change from baseline in FACIT fatigue scores
Secondary estimand 5	Change from baseline in reticulocytes counts**	Treatment policy	Treatment policy	Treatment policy	Treatment policy	Mean change from baseline in reticulocyte counts
Sensitivity analysis (Secondary) 5.1	Change from baseline in reticulocytes counts**	Treatment policy Missing reticulocyte central lab data replaced by local lab data at same visit.	Treatment policy	Treatment policy	Treatment policy	Mean change from baseline in reticulocyte counts

Estimand	Endpoint	Handling strategy of intercurrent events				Summary measure
		Missing data on iptacopan after study discontinuation imputed using "return to pre-treatment"				
Supportive estimand (Secondary) 5.1	Change from baseline in reticulocytes counts**	Treatment policy	Treatment policy	Treatment policy	Hypothetical Policy	Mean change from baseline in reticulocyte counts
Secondary estimand 6	Percent change from baseline in LDH**	Treatment policy Missing data on iptacopan after study discontinuation imputed using "return to pre-treatment"	Treatment policy	Treatment policy	Treatment policy	The log transformed LDH ratio to baseline
Sensitivity analysis 6.1	Percent change from baseline in LDH**	Treatment policy Missing LDH central lab data replaced by local lab data at same visit. Missing data on iptacopan after study discontinuation imputed using "return to pre-treatment"	Treatment policy	Treatment policy	Treatment policy	The log transformed LDH ratio to baseline
Supportive estimand (Secondary) 6.1	Percent change from baseline in LDH**	Treatment policy Missing data on iptacopan after study discontinuation imputed using "return to pre-treatment"	Treatment policy	Treatment policy	Hypothetical Policy	The log transformed LDH ratio to baseline
Secondary estimand 7	Rates of breakthrough hemolysis	Treatment policy	Not an intercurrent event since this is the endpoint of interest	Treatment policy	Treatment policy	Rate of occurrence of breakthrough hemolysis
Secondary estimand 8	Rates of MAVE s	Treatment policy	Treatment policy	Not an intercurrent event since this is the endpoint of interest	Treatment policy	Rate of occurrence of MAVEs

* between Day 126 and 168 (3 out of 4 scheduled measurements)

** between Day 126 and 168

between Day 14 and Day 168

$between Day 1 and Day 168

f rescue indicates failure

5.2.2 Primary analysis

5.2.2.1 MMRM convergence issue

For MMRM, by default, the correlations between visits (aka. Timepoints) within subjects will be modeled using an unstructured covariance matrix.

In case of non-convergence issues the following steps should be taken:

- Simplify covariance structure (possibly AR(1) then CS)
- Simplify the model by removing some covariates (baseline value should always be kept in the model and visit x baseline value interaction can for instance be first removed)

5.2.2.2 Methods for calculation of marginal proportions and simple proportion

Marginal proportion from Logistic regression

The primary analysis of the primary endpoint will be a logistic regression to estimate the response probability.

$$\log\frac{P(Y=1)}{1-P(Y=1)} = \beta_0 + \beta_1 S + \beta_2 A + \beta_3 H + \beta_4 T$$

Where $P(Y=1)$ refers to the probability to be responder, S refers to sex, A refers to indicator variable of age $\geq$ 45 years, H refers to indicator variable of baseline hemoglobin above 8g/dL and T refers to an indicator of transfusion dependence.

The maximum likelihood estimator for $\hat{\beta}_0, \hat{\beta}_1, \hat{\beta}_2, \hat{\beta}_3, \hat{\beta}_4$ will be plugged in to obtain the probability to be a responder for each participant

$$\hat{\theta}_i = \hat{P}(Y_i = 1) = \frac{\exp[\widehat{\beta}_0 + \hat{\beta}_1 S_i + \hat{\beta}_2 A_i + \hat{\beta}_3 H_i + \hat{\beta}_4 T_i]}{1 + \exp[\widehat{\beta}_0 + \hat{\beta}_1 S_i + \hat{\beta}_2 A_i + \hat{\beta}_3 H_i + \hat{\beta}_4 T_i]}$$

The proportion of responders will be derived from the estimated marginal probabilities ($\hat{\theta}$) derived from the model fit as the mean of the individual logistic regression model predictions,

$$\hat{\theta} = \frac{\sum_{i=1}^{N} \hat{\theta}_i}{N}$$

The 95% confidence intervals will be derived by the bootstrap method (Steingrimsson et al 2017). Take B bootstrap samples of (Y, S, A, H, T). For each bootstrap sample, obtain the proportion of responders. Then we will have B estimators, denoted to be $\theta_1^{\{b\}}$, $\theta_2^{\{b\}}$, …, $\theta_B^{\{b\}}$.

The 95% confidence interval is the 2.5% quantile and 97.5% quantile of these bootstrap estimator.

In case of multiple imputation, the marginal probability and the associated two-sided 95% confidence intervals will be obtained by combining multiple imputations with bootstrapping as follows:

1) Point estimate will be obtained by averaging across the estimates obtained from each multiple imputed dataset
2) The 95% confidence interval will be obtained by bootstrapping each imputed dataset and selecting the 2.5th and 97.5th percentiles of the pooled distribution of bootstrapped parameter estimates as the confidence interval bounaries.

Simple proportion

For each imputed dataset, proportion of responders is

$$\theta_j = \frac{\sum_{i=1}^{N} Y_i}{N},$$

where $Y_i = 1$ denotes a participant is responder while $Y_i = 0$ denotes a participant is non-responder. Denote the number of imputed dataset to be L and denote θ_j $(j = 1, \dots, L)$ to be the proportion of responders for each imputed dataset, simple proportion of responders is the mean of proportion of responders from all the imputed datasets, that is

$$\hat{\theta} = \frac{\sum_{j=1}^{L} \theta_j}{L}$$

The 95% confidence intervals will be derived by the bootstrap method (Steingrimsson et al 2017). For each bootstrap sample, obtain the simple proportion of responders. Then we will have B estimators, denoted to be $\theta_1^{\{b\}}$, $\theta_2^{\{b\}}, \dots,$ $\theta_B^{\{b\}}$. The 95% confidence interval is the 2.5% quantile and 97.5% quantile of these bootstrap estimator.

In case of multiple imputation, the simple proportion of responders and the associated two-sided 95% confidence intervals will be obtained by combining multiple imputations with bootstrapping as follows:

1) Point estimate will be obtained by averaging across the estimates obtained from each multiple imputed dataset
2) The 95% confidence interval will be obtained by bootstrapping each imputed dataset and selecting the 2.5th and 97.5th percentiles of the pooled distribution of bootstrapped parameter estimates as the confidence interval bounaries.

It can be shown that the estimate of the marginal probabilities from logistic regression model and simple estimate of the response probability without any covariates are the same.

From logistic regression,

$$\theta_i = \Pr(Y_i = 1 | S_i, A_i, H_i, T_i) = \frac{\exp\left[\beta_0 + \beta_1 S_i + \beta_2 A_i + \beta_3 H_i + \beta_4 T_i\right]}{1 + \exp\left[\beta_0 + \beta_1 S_i + \beta_2 A_i + \beta_3 H_i + \beta_4 T_i\right]}$$

The loglikelihood is

$$Loglikelihood = \sum_{i=1}^{N} \log[1-\theta_i] + (\beta_0 + \beta_1 S_i + \beta_2 A_i + \beta_3 H_i + \beta_4 T_i) Y_i$$

Take the derivative of the log likelihood function with respective to β_0, and let it equal to 0 to obtain

$$\frac{1}{N}\sum_{i=1}^{N} \theta_i = \frac{1}{N}\sum_{i=1}^{N} Y_i$$

This indicates that point estimate of the marginal probability from the logistic regression model and the simple response probability without the covariates are the same.

The 95% confidence intervals from logistic regression model and the simple response probability will be obtained by selecting the 2.5th and 97.5th percentiles of the same pooled distribution of bootstrapped parameter estimates. Therefore, the confidence interval will also the same for the estimates obtained from the logistic regression model and simple proportion.

5.2.2.3 Derivation of the threshold

As the patient-level hemoglobin data were not available for the historical eculizumab/ravulizumab studies, a direct estimation of the proportion of patients who achieved hemoglobin increases from baseline ≥ 2 g/dL in the absence of transfusions (responder definition on primary efficacy endpoint for study CLNP023C12301) was not feasible. Therefore, an indirect approach through simulation calculating the probability of being a responder (defined as increase from baseline of hemoglobin ≥ 2 g/dL) was used.

Overview of reference studies

This 15% threshold was derived by indirectly estimating hemoglobin response in two studies with eculizumab: Study ALXN1210-PNH-301 (Ultomiris CHMP Assessment Report 2019, Lee et al 2019, Brodsky et al 2021) that included a treatment naive population randomizing patients to either eculizumab or ravulizumab and the pivotal eculizumab study, TRIUMPH (Hillmen etal 2006, Dmytrijuk et al 2008)

ALXN1210-PNH-301 was a Phase 3, open-label study that assessed the non-inferiority of ravulizumab to eculizumab in complement inhibitor-naive adults with PNH. The study recruited PNH patients ≥ 18 years of age, with red and white blood cells with granulocyte or monocyte clone size of at least 5%, with LDH ≥ 1.5 times the upper limit of normal, with at least one protocol pre-defined PNH-related sign or symptom and with platelet count ≥ 30 X 10E9/L or absolute neutrophil count ≥ 0.5 X 10E9/L. Patients were randomized 1:1 to receive ravulizumab or eculizumab for 183 days (N = 246). Co-primary efficacy endpoints were proportion of patients remaining transfusion-free and LDH normalization. Key secondary endpoints were percentage change from baseline in LDH, change from baseline in FACIT-Fatigue score, proportion of patients with breakthrough hemolysis, and proportion of patients with stabilized hemoglobin (defined as avoidance of a ≥ 2 g/dL decrease in hemoglobin level from baseline in the absence of transfusion). 69 (57.0%) of 121 PNH patients who were treated with eculizumab were male. The mean age at first study infusion was 46.2 (SD: 16.2). 105 (86.8%) patients had an LDH ratio > 3x ULN. The mean LDH at baseline was 1578.3 U/L (SD: 727.1). 21 (17.4%)

patients received no packed RBC transfusion within 1 year before study entry, and 22 (18.2%) patients received > 14 units of packed RBC within 1 year before study entry.

TRIUMPH was a double-blind, randomized, placebo-controlled, multicenter, Phase 3 trial. The trial consisted of a 2-week screening period, an observation period of up to 3 months, and a 26-week treatment period. Patients 18 years of age or older who had received at least four transfusions during the previous 12 months were eligible. A PNH type III erythrocyte proportion of 10% or more, platelet counts of at least 100,000 per cubic millimeter, and LDH levels that were at least 1.5 times the upper limit of the normal range were also required. The two primary endpoints were the stabilization of hemoglobin levels (defined as a hemoglobin value maintained above the level qualifying for transfusion, in the absence of transfusions during the 26-week treatment period), and the number of units of packed red cells transfused during the period. 23 (53.5%) of 43 patients who were treated with eculizumab were female. In the eculizumab group, the mean age at baseline was 41.0 (Range: 20-85) and the mean LDH at baseline was 2199.7 U/L (SD: 157.2 U/L). In the 6-month period before the study, the median number of units of packed red cells transfused per patient was 9.0 in the eculizumab cohort and the mean number of units of packed red cells transfused was 9.6 ± 0.6

Assumptions for simulation and statistical aspects

The assumptions used for simulation based on ALXN1210-301 data are summarized below:

- Mean hemoglobin level at baseline was 9.6 g/dL from Brodsky et al 2021,
- Mean hemoglobin level at Week 26 was 10.0 g/dL from Figure 20 of Ultomiris CHMP Assessment Report 2019,
- Standard deviations of hemoglobin at baseline (Brodsky et al 2021) and Week 26 were assumed to be equal and the value was 1.70 g/dL

The assumptions used for simulation based on TRIUMPH (Hillmen et al 2006) data are summarized below:

- Mean hemoglobin level at baseline was 10.0 g/dL
- Mean hemoglobin level at Week 26 was 10.1 g/dL
- Standard deviation of hemoglobin at baseline and Week 26 was assumed to be equal and the value was calculated as $0.2\sqrt{43} = 1.31$ g/dL, where 0.2 g/dL was the standard error of mean

The correlation value between hemoglobin level at baseline and at Week 26 was not available from published historical studies. This value was derived based on Hillmen et al 2004 which published hemoglobin levels before 12 months eculizumab treatment and after 3 months of eculizumab treatment for 11 PNH patients. The correlation was 0.87 for these 11 PNH patients. Considering the same sample size and different treatment periods, for simulation purposes, correlation values were drawn from a uniform distribution Unif (0.3, 0.85).

Under the normal distribution assumption for hemoglobin data, patients' hemoglobin values at baseline and at Week 26 were drawn from a bivariate normal distribution:

$$\begin{pmatrix} x_{1i} \\ x_{2i} \end{pmatrix} \sim N\left[\begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, \begin{pmatrix} \sigma_1^2 & \rho\sigma_1\sigma_2 \\ \rho\sigma_1\sigma_2 & \sigma^2{}_2 \end{pmatrix}\right], \mathrm{i} = 1, \ldots, \mathrm{N}$$

where μ_1 is the mean of hemoglobin level at baseline, μ_2 is the mean of hemoglobin level at Week 26, σ_1 is the standard deviation of hemoglobin at baseline, σ_2 is the standard deviation of hemoglobin at Week 26, and ρ is the correlation. The proportion of drawn hemoglobin values that demonstrate increase from baseline in hemoglobin of ≥ 2 g/dL based on N draws from the bivariate normal distribution is summarized:

$$Proportion\ of\ Response = \frac{1}{N}\sum_{i}^{N} I[x_{2i} - x_{1i} \geq 2],\ \ I\ is\ the\ indicator\ function$$

Results of simulation and inference

10000 simulation runs indicate that the probability of being a responder (achieving a hemoglobin increase from baseline ≥ 2 g/dL) is 14.7% (95% CI: 5.0% - 21.1%) for ALXN1210-301 study, and 4.49% (95% CI: 0.5% - 11.0%) for TRIUMPH.

Please note that these estimates (14.7% and 4.49%) actually overestimate the hematological effect for eculizumab because the hemoglobin levels correspond to all patients at Week 26, and doesn't account for administration of transfusion during treatment.

Despite being aware of the overestimate of the hematological effect, the 15% threshold was chosen in order to be above the estimated hemoglobin increases in both historical studies. Thus, exceeding this threshold is sufficient to demonstrate that iptacopan improves the hematological response in PNH patients with hemolysis and anemia in the absence of transfusions.

5.2.3 Rule of exclusion criteria of analysis sets

Considering the relatively low sample size in the study there are no protocol deviations which will lead to exclusion of patients from any analysis set. Data records containing confirmed cases of biological sample analysis after Withdrawal of Consent, when not allowed per ICF or local regulations, will be flagged and excluded from all analyses including listings.

6 Reference

Brodsky RA, Peffault de Latour R, Rottinghaus ST, Roth A, Risitano AM, Weitz IC, Hillmen P, Maciejewski JP, Szer J, Lee JW, Kulasekararaj AG, Volles L, Damokosh AI, Ortiz S, Shafner L, Liu P, Hill A, Schrezenmeier H. Characterization of breakthrough hemolysis events observed in the phase 3 randomized studies of ravulizumab versus eculizumab in adults with paroxysmal nocturnal hemoglobinuria. Haematologica. 2021 Jan 1; 106(1): 230-237.

Patricia Berglund and Steven Heeringa (2014) Multiple imputation of missing data using SAS. SAS Institute

Committee for Medicinal Products for Human USE (CHMP) (2019) Ultomiris Assessment Report. European Medicines Agency.

Cro Suzie, Morris Tim, Kenward Michael, and Carpenter James (2020) Sensitivity analysis for clinical trials with missing continuous outcome data using controllled multiple imputation: A practical guide. Statistics in Medicine, 2020; 39: 2815-2842.

Dmytrijuk, A., Robie-Sun, K., Cohen, M.H., Rieves, D., Weiss, K., Pazdur, R. (2008) FDA Report: Eculizumab (Soliris) for the Treatment of Patients with Paroxysmal Nocturnal Hemoglobinuria. *The Oncologist*; 13:993-1000.

[redacted]

Garwood, F (1936). Fiducial limits for the Poisson distribution. Biometrika, 46; 441–453.

Hillmen, P., Yong, N.S., Schubert, J.,Brodsky, R.A., Socie, G., Muus, P., Roth, A., Szer, J., Elebute, M.O., Nakamura, R., Browne, P., Risitano, A.M., Hill, A., Schrezenmeier, H., Fu, C.L., Maciejewski, J., Rollins, S.A., Mojcik, C.F., Rother, R.P. & Luzzatto, L. (2006) The complement inhibitor eculizumab in parxoxysmal nocturnal hemoglobinuria. *New England Journal of Medicine*, 355, 1233-1243.

Lee, J.W., Fontbrune, F.S., Lee, L.W.L., Pessoa, V., Gualandro. S., Fureder, W., Ptushkin. V., Rottinghaus, S.T., Volles. L, Shafner. L., Aguzzi. R., Pradhan, R., Schrezenmeier, H., Hill, A. (2019) Ravulizumab (ALXN1210) vs. Eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. *Blood* Volume 133, Number 6.

Xinghe, Lu (2016) Correcting the quasi-complete separation issue in logistic regression models. AmeriHealth Caritas. Mathematics

Miettinen and Nurminen. (1985) Comparative analysis of two rates. *Statistics in Medicine* Volume 4 213-226.

Nelson, W (1995) Confidence Limits for Recurrence Data—Applied to Cost or Number of Product Repairs. Technometrics; 37: 147–157.

Ratitch, Bohdana and O'Kelly Michael (2011) Implementation of Pattern-Mixutre Models Using Standard SAS/STAT Procedures. PharmaSUG2011-Paper SP04.

Sahai H, Khurshid Anwer (1993). Confidence intervals for the mean of a poisson distribution: a review. Biom J, 35 (7); 857-867.

Scosyrev E. Asymptotically robust variance estimation for person-time incidence rates. Biom J. 2016 May;58(3):474-88.

Scosyrev E, Pethe A. Confidence intervals for exposure-adjusted rate differences in randomized trials. Pharm Stat. 2022 Jan;21(1):103-121