NOVARTIS

Clinical Development

LNP023/Iptacopan

CLNP023C12303 / NCT05630001

A multicenter, single arm, open-label trial to evaluate efficacy and safety of oral, twice daily iptacopan in adult PNH patients who have Hb≥10 g/dL in response to anti-C5 antibody and switch to iptacopan

Statistical Analysis Plan (SAP) Amendment 2

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
17-Apr-2023	Prior to FPFV	N/A	N/A - First version	NA
	Prior to dry run	Analyses changed	Clarifying that the proportion of responders with Hb >= 12 g/dL will be handled by a composite strategy	Section 1.3.2
	Prior to dry run	Analyses changed	Adding more details to the definition and handling of missing data for baseline Hb value and FACIT-Fatigue score for efficacy analyses	Section 2.1.1.3
	Prior to dry run	Analyses changed	Adding more details to the definition of on-treatment period Adding descriptive analysis for on-treatment period, study treatment period and duration of follow-up	Section 2.1.1.5
	Prior to dry run	Analyses changed	Adding more details to unscheduled visits	Section 2.1.1.6
	Prior to dry run	Analyses changed	Adding geographical region to subgroup of interest	Section 2.2.1
	Prior to dry run	Analyses changed	Clarifying the definition of current medical conditions at baseline and adding listing of medical history Removing transfusion and hemoglobin history from baseline analysis	Section 2.3.3
	Prior to dry run	Analyses changed	Adding definition of missed dose Adding analyses for dose intensity categories and relative dose intensity categories Modifying analysis of duration of treatment period to duration of treatment	Section 2.4.1
	Prior to dry run	Analyses changed	Adding more details for the analysis of concomitant medications	Section 2.4.2
	Prior to dry run	Analyses changed	Modifying the language for the analysis of primary endpoint	Section 2.5.1
	Prior to dry run	Analyses changed	Modifying the language for using hypothetical strategy to handle intercurrent events for primary endpoint	Section 2.5.4

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
	Prior to dry run	Analyses changed	Adding definition of cohort for whom the occurrent of BTH, MAVE events and RBC transfusions will be graphically presented if applicable; Changing graphical presentation to descriptive summary for observed Hb values over time Adding a graph showing the trend of Hb values	Section 2.5.8
	Prior to dry run	Analyses changed	Moving multiplicity adjustment to a new section	Section 2.6.1.2
	Prior to dry run	Analyses changed	Clarifying proportion of transfusion avoidance will be estimated based on observed data rather than imputed datasets Adding methods for the calculation of 95% CI for transfusion avoidance (Wilson methods)	Section 2.6.1.4
	Prior to dry run	Analyses changed	Changing graphical presentation to descriptive summary for observed ARC and LDH values	Section 2.6.1.5, Section 2.6.1.6
	Prior to dry run	Analyses changed	Changing the methods for the analysis of TSQM-9 scores	Section 2.6.1.7
	Prior to dry run	Analyses changed	Clarifying imputed Hb values will not be used to make decision on whether patients quality for meeting transfusion criteria	Section 2.6.3
	Prior to dry run	Analyses changed	Adding shift tables for biochemistry parameters that are not CTCAE graded; Adding separate listing for hematology, biochemistry and urinalysis; Modifying the definition of liver toxicities based on latest MAP document	Section 2.7.3
	Prior to dry run	Analyses added	Including notable criteria for vital signs	Section 2.7.5
	Prior to dry run	Anlyses added	Adding more details for the analyses of biomarkers	Section 2.11
	Prior to dry run	Analyses changed	Changing graphical presentation to descriptive summary for hematologcial parameters	Section 2.13
	Prior to dry run	Analyses changed	Modifying changes to protocol-specified analyses	Section 4

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
	Prior to dry run	Analyses changed	Removing sensitivity analysis as the proportion of patients with transfusion avoidance will be calculated based on observed data rather than imputation	Section 5.2.1
	Prior to dry run	Analyses changed	Removing multiple imputation for FACIT-Fatigue score and complete case analysis will be performed	Section 5.2.1
	Prior to dry run	Analyses changed	The methods of missing data imputation for handling Hb data within 30 days of transfusion are changed to missing at random approach (MAR)	Section 5.2.3
	Prior to dry run	Analyses changed	Adding more details to the missing data handling for proportion of participants achieving sustained Hb levels ≥ 12g/dL without transfusions	Section 5.2.4
	Prior to DBL	Analyses changed on team request	Adding analysis for history of aplastic anemia Removing analysis for WBC clone size	Section 2.3.3
	Prior to DBL	Details added for handling early study discontinuation and imputation methodology	Adding handling methods for missing Hb data after early study discontinuation. Adding handling methods for patients who have early treatment discontinuation but remain in study until EoS Imputation model slightly updated by removing age, sex.	Section 2.5.4 Section 2.5.5 Section 2.5.7
	Prior to DBL	Alignment with project level Master Analysis Plan (MAP)	Adding Table 2-2 for definition of symptoms and AEs for liver toxicities	Section 2.7.3
	Prior to DBL	Analyses added based on team request.	Adding analyses for additional biomarkers such as Factor B, fragment Bb and sC5B9. Handling of LLOQ and ULOQ added.	Section 2.11
	Prior to DBL	Detail modified based on team request	Description changed to reflect the new system (SDMS) for AESI	Section 2.7.1.1
	Prior to DBL	Analyses changed	Outcome measure of TSQM-9 changed to change from baseline and MMRM model is used for analysis	Section 1.3.2
	Prior to DBL	Analyses removed	Descriptive statistics for on-treatment period are removed from analysis	Section 2.1.1.5

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
	Prior to DBL	Details modified based on team request	Analyses related to certain classes of prior and concomitant medications are removed	Section 2.4.2
	Prior to DBL	Analyses added based on team request	Analyses added for additional biomarker parameters	Section 2.11
	Prior to DBL	Details added for SAS procedure MIANALYZE and Rubin's rule	Description added to clarify the handling way for calculation of overall estimates across imputed datasets when there is no missing values reported for a given visit	Section 5.2.5

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AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
aPTT	Activated partial thromboplastin time
ARC	Absolute Reticulocyte Count
AST	Aspartate Aminotransferase
b.i.d.	bis in die/twice a day
BP	Blood Pressure
BTH	Breakthrough Hemolysis
CTCAE	Common Terminology Criteria for Adverse Events
CI	Confidence Interval
CK	Creatine Kinase
COVID-19	Coronavirus Disease 2019
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical Study Report
CV	Coefficient of Variation
DMC	Data Monitoring Committee
CCI	[redacted]
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EoS	End of Study
ETD	Early Treatment Discontinuation
EVH	Extravascular Hemolysis
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full Analysis Set
FDA	Food and Drug Administration
g	Gram
h	Hour
Hb	Hemoglobin
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
INR	International Normalized Ratio
IVH	Intravascular Hemolysis
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit Of Quantification
MAP	Master Analysis Plan
MAVE	Major Adverse Vascular Event
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
mL	milliliter(s)
MMRM	Mixed Model for Repeated Measures

NI	Non-inferiority
CCI	[redacted]
CCI	[redacted]
PNH	Paroxysmal Nocturnal Hemoglobinuria
PRO	Patient Reported Outcomes
PT	Preferred Term
CCI [redacted]	[redacted]
QTcF	QT interval corrected by Fridericia's formula
RBC	Red Blood Cell
REP	Roll-over Extension Program
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SCR	Screening Set
SD	Standard Deviation
SoA	Schedule of Activities
SoC	Standard of Care
SOC	System Organ Class
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	Upper Limit of Normal
ULOQ	Upper Limit Of Quantification
WBC	White Blood Cell
WHO	World Health Organization

1 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses as outlined in the Clinical Trial Protocol (CTP) Version 02. The analyses in this SAP will be used to support the completion of the final Clinical Study Report (CSR) for the CLNP03C12303 study when the last participant has completed the study.

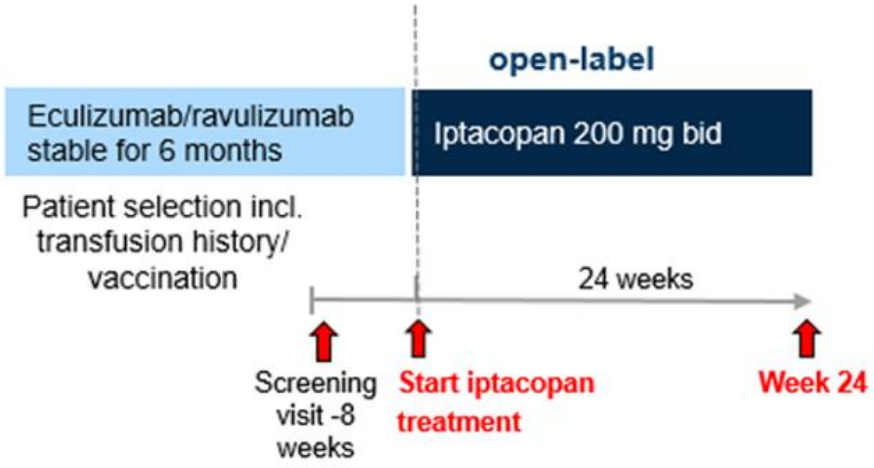
1.1 Study design

This is a multicenter, single-arm, open label trial, with iptacopan treatment for 24 weeks in adult PNH patients. A diagram of the study design is shown in Figure 1-1. Eligible participants must have a mean Hb ≥10 g/dL in response to a stable regimen with anti-C5 for at least 6 months before screening (and during screening) and must be RBC transfusion free for the same period. This study is comprised of two periods:

- A **Screening period** lasting up to 8 weeks.
- A 24-week open-label, iptacopan **Treatment period**.

A total of approximately 50 participants will be enrolled in the trial. All participants must provide written informed consent prior to start of any study-related activities.

Figure 1-1 Study design diagram



Screening period

Screening period starts at the time of Informed Consent Form (ICF) signing and lasts until the day preceding Day 1 of the 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 enrollment into the study at screening visit 1. If a participant meets eligibility criteria during screening visit 1, screening visit 2 will be performed to confirm hemoglobin as per inclusion criterion 4 and vaccination status as per inclusion criteria 5 and 6 defined in **Section 5.1 in the CTP**. This will be followed by assessments as outlined in the schedule of activities (SoA) in the CTP, as applicable.

By signing the ICFs, the participants will provide access to the following medical records for the last 6 to 12 months prior to Screening:

- Date and result of PNH WBC clone size performed in the 12 months prior to Screening.
- Hb levels, MAVEs and anti-C5 antibody regimen reported in the past 6 months.
- The number of transfusions and unit numbers of packed RBC received in the past 12 months.

If eligibility criteria are not met due to any assessment, the participant should be considered as having failed the screening and does not proceed to treatment period. In the case where a safety laboratory value at screening is outside of the range specified in the exclusion criteria, the assessment may be repeated once, before participant is considered to have failed screening. The participant can be rescreened once as described in the CTP.

Treatment period

Participants who meet all the eligibility criteria will proceed to the treatment period. Treatment with iptacopan at a dose of 200 mg b.i.d. will start on the first day (Day 1) and should continue for 24 weeks with study visits and corresponding assessments according to the SoA described in the CTP.

For participants who permanently discontinue iptacopan administration, close monitoring and treatment proposals as described in the CTP is required. Every effort must be made to keep participants in the study to complete visits and assessments up to the Day 168 visit as defined in the SoA in the CTP. Formal definitions of the on-treatment period, study treatment period and follow-up period are provided in Section 2.1.1.5.

Study completion and roll-over extension program (REP)

Study completion is defined as when the last participant completes their End of Study (EoS) visit (Day 168 visit), and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision. After completion of the treatment period, participants who complete this trial while still receiving iptacopan and who continue to derive clinical benefit from the treatment based on the Investigator's evaluation will be able to join the roll-over extension program (REP; CLNP023C12001B). Participants that do not continue in the REP, should be monitored for AEs as described in the CTP.

Early Treatment Discontinuation (ETD) and follow-up visits

Permanent treatment discontinuation is defined as discontinuing treatment before the EoS visit (Day 168 visit). Participants who permanently discontinue study medication during the treatment period, should complete the Early Treatment Discontinuation (ETD) visit, follow-up visit 1 and follow-up visit 2 and visits as scheduled up to the Day 168 visit. If they fail to return for these assessments for unknown reasons, every effort (e.g., telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section in the CTP. This contact should preferably be done according to the study visit schedule.

1.2 Study population

This study will enroll adult PNH patients (≥ 18 years) with Hb ≥10 g/dL (mean of all Hb assessments [minimum two] collected 6 months prior to screening as defined in the inclusion criteria in the CTP) in response to anti-C5 antibody treatment on stable regimen (dose and intervals) for at least 6 months, and who did not receive any RBC transfusions in the previous 6 months as well as during screening. In addition, prior to starting iptacopan treatment, participants must have two different Hb samples collected during the screening period and evaluated by the central laboratory with mean Hb ≥10 g/dL. The definition of the baseline Hb value for analysis purposes is provided in Section 2.1.1.3.

The study targets enrollment of at least 60% of patients with mean Hb <12 g/dL at screening, therefore the number of patients with mean Hb ≥ 12 g/dL at screening will be restricted to maximum 40%.

1.3 Study objectives, endpoints and estimands

Table 1-1 Study objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
● To demonstrate non-inferiority of iptacopan after switching from SoC (anti-C5) in Hb change from baseline.	● Change in Hb levels as mean of visits between Day 126 and Day 168 compared to baseline, defined as mean of Hb collected at screening (two samples) and Day 1.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
● To demonstrate superiority of iptacopan after switching from SoC (anti-C5) in Hb change from baseline.	● Change in Hb levels as mean of visits between Day 126 and Day 168 compared to baseline, defined as mean of Hb collected at screening (two samples) and Day 1.
● To assess the percentage of hematological responders to iptacopan treatment defined as Hb ≥12 g/dL in the absence of RBC transfusions	● Response defined as Hb ≥12 g/dL on three out of four measurements taken at the visits occurring in the last six weeks (between Day 126 and Day 168) in the absence of RBC transfusions (between Day 1 and Day 168)
To assess the effect of iptacopan on transfusion avoidance defined as the proportion of participants who remain free from transfusions.	Proportion of patients with absence of administration of packed RBC transfusions and not requiring RBC transfusions between Day 1 and Day 168.
● To assess the effect of iptacopan on markers of EVH and IVH.	● Change from baseline in ARC levels as mean of visits between Day 126 and Day 168 ● Percentage change from baseline in LDH levels as mean of visits between Day 126 and Day 168.
● To assess the patients' perceived differences in global satisfaction, effectiveness and convenience between baseline and Day 84 and Day 168 after switching from SoC (anti-C5) to iptacopan	● Difference in scores of the global satisfaction, effectiveness, and convenience domains of the Treatment Satisfaction Questionnaire for Medication (TSQM-9) between baseline and Day 84 and Day 168 assessed after switching from SoC (anti-C5) to iptacopan
● To assess changes in patient-reported fatigue from baseline to Day 84 and Day 168	● Change from baseline in patient-reported scores for FACIT-F collected at Day 84 and Day 168
● To assess the frequency of BTH through Day 168	● Occurrences of BTH reported between Day 1 and Day 168

Objective(s)	Endpoint(s)
● To assess the frequency of Major Adverse Vascular Events (MAVEs including thrombosis) of iptacopan through Day 168	● Occurrences of MAVEs occurring between Day 1 and Day 168
● To assess the 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
CCI	CCI
● CCI	CCI

1.3.1 Estimand for primary and key secondary objective

The primary clinical question is the following: what is the treatment effect of iptacopan after 24 weeks compared to baseline in PNH patients who have Hb ≥10 g/dL in response to stable regimen of anti-C5 antibody treatment, regardless of discontinuation of iptacopan and occurrence of breakthrough hemolysis (BTH) or Major Adverse Vascular Events (MAVEs)?

The attributes of the estimand for the primary and key secondary objective are:

- **Population**: PNH patients ≥ 18 years on stable regimen of anti-C5 treatment and with Hb levels stable ≥10 g/dL, without any RBC transfusion in the past 6 months.
- **Treatment of interest:** the investigational treatment iptacopan at a dose of 200 mg b.i.d. regardless of whether the participant discontinues treatment (treatment policy).
- **Intercurrent events**: discontinuations of study medication for any reason, BTH events, and MAVEs will be handled with a treatment policy strategy. RBC transfusions will be handled using a hypothetical strategy, as if participant would not have received transfusions on iptacopan treatment.
- **Summary measure**: the mean change from baseline in Hb and it's 95% CI.

The primary objective of the study is to demonstrate non-inferiority (NI) of iptacopan over SoC and the key secondary objective is to demonstrate superiority. The testing strategy is described in Section 2.6.1.2.

Table 1-2 Justification of handling of intercurrent events

Intercurrent event	Handling strategy	Justification
Treatment discontinuation	Treatment policy	The effect of treatment will be assessed even when participants discontinue study treatment. Data collection will be maintained, and all available measurements after treatment discontinuation will be used for analysis.
BTH events	Treatment policy	The effect of treatment will be assessed. BTH may affect the endpoints of interest, hence data collection will be maintained, and available measurements collected during and after BTH will be used for analysis.
MAVEs	Treatment policy	The effect of treatment will be assessed, in particular in presence or after the occurrence of MAVEs. Data collection will be maintained, and available measurements collected during and after MAVEs will be used for analysis.
RBC transfusions	Hypothetical strategy	The effect of RBC transfusions are not of interest. The treatment will be assessed as if participant would not have received RBC transfusions. Hb data 30 days after RBC transfusion will be excluded and imputed using a hypothetical strategy as though RBC transfusion were not administered. RBC transfusions are expected to be rare.

1.3.2 Secondary estimands

The population and intercurrent events associated with the remaining secondary estimands are the same as for the primary and key secondary estimand. Treatment discontinuations, BTH events, and MAVEs will be handled using a treatment policy strategy. For secondary endpoints based on Hb levels, RBC transfusions will be handled by a hypothetical strategy as for the primary endpoint. The proportion of responders with Hb ≥12 g/dL on three out of four measurements taken at the visits occurring in the last six weeks (between Day 126 and Day 168) will be handled by a composite strategy. For all other secondary endpoints (apart from the proportion of patients with transfusion avoidance), RBC transfusions will be handled by a treatment policy.

In brief, the remaining secondary estimands are defined as follows:

- Response defined as Hb ≥12 g/dL on three out of four measurements taken at the visits occurring in the last six weeks (between Day 126 and Day 168) in the absence of RBC transfusions (between Day 1 and Day 168). The summary measure is the proportion of responders.
- Absence of administration of packed-RBC transfusions between Day 1 and Day 168: proportion of participants not receiving and not requiring any transfusions between Day 1

and Day 168 (transfusion avoidance). The summary measure is the proportion of responders.

- Change from baseline in absolute reticulocyte counts (ARC) as mean of visits between Day 126 and Day 168. The summary measure is the mean change from baseline of ARC levels.
- Percent change from baseline in LDH between Day 126 and Day 168. The summary measure is derived from the mean of the log-transformed ratio to baseline in LDH between Day 126 and Day 168.
- Difference in scores of the global satisfaction, effectiveness, and convenience domains of the TSQM-9 between baseline and Day 84 and Day 168 assessed after switching from SoC (anti-C5) to iptacopan. The summary measure is the mean change from baseline in patient-reported scores (for each of the three TSQM-9 domains).
- Change from baseline in patient-reported scores for FACIT-F collected at Day 84 and Day 168. The summary measure is the mean change from baseline in patient-reported scores for FACIT-F.
- Rates of occurrences of BTH reported between Day 1 and Day 168. The summary measure is occurrences per year.
- Rates of occurrences of MAVEs occurring between Day 1 and Day 168. The summary measure is occurrences per year.

2 Statistical methods

2.1 Data analysis general information

Analyses will be performed by the Sponsor. The most recent version of SAS® and R software available in the statistical programming environment will be used for the analysis. Periodic safety reviews for monitoring safety data will be performed internally. A DMC is functioning at the iptacopan program level and SAEs might be presented ad hoc to the DMC members.

For categorical variables, the absolute number of participants (N) in each category and absolute and relative frequencies will be provided. For continuous data, N, mean, standard deviation (SD), median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented. Log-transformation refers to the natural logarithm (base e) unless otherwise specified.

For all efficacy analyses based on laboratory data addressing primary and secondary objectives (e.g., hemoglobin, reticulocytes etc.), the information obtained from the central lab will be used. Sensitivity analyses will be performed where missing central lab data will be replaced by local lab data as specified in Section 2.5, Section 2.6, and Table 5-1 in the Appendix.

2.1.1 General definitions

2.1.1.1 Investigational treatment/investigational drug

The term **investigational treatment** or **investigational drug** refers to iptacopan 200 mg capsules administered twice daily (b.i.d.).

The term **date of first administration of investigational drug/treatment** refers to the date of first dosing of participants with study drug/treatment during the study.

The term **date of last administration of study drug/treatment** refers to the date of last actual administration of any study drug/treatment in the study.

2.1.1.2 Study day

The term **study day** is defined relative to the analysis reference date, which is the date of first administration of study treatment (Day 1). The day before the first dose of investigational treatment is defined as Day -1 (there is no Day 0).

The study day for a scheduled or unscheduled visit **on or after** the analysis reference date (date of Day 1) is defined as:

Study day= (Date of Visit) – (analysis reference date) +1

The study day for a scheduled or unscheduled visit **before** the analysis reference date is defined as:

Study day = (Date of visit) – (analysis reference date).

In case participants did not receive any study treatment, **one day after** the date of completion of screening assessments will be used as the analysis reference date (Day 1).

2.1.1.3 Baseline definitions

For the analysis of efficacy and safety data based on the FAS and SAF as defined in Section 2.2, the baseline value for baseline demographics, medical history, laboratory values, vital signs and ECGs is defined as the last result obtained prior or at the start of study treatment (Day 1). As per CTP, all assessments on Day 1 are to be performed before the administration of the first dose. Most variables will have their baseline at Day 1 (before the administration of the first iptacopan dose) unless otherwise specified. 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. Rules for identifying baseline values in case the Day 1 assessment is missing are defined in Table 5-2.

The baseline Hb value for efficacy analyses is defined as the mean of three Hb assessments conducted at the central laboratory: two during screening and the third on Day 1. For patients where Hb from second screening visit is missing, the Hb from first unscheduled visit (if any) performed at central lab after Screening visit 1 and before Visit 101 will be used to map the value for Hb as Screening visit 2. Note that the unplanned visit for mapping must occur prior to the initiation of study treatment. In case of missing data (Hb values are missing for any of

the three scheduled visits without any unplanned visit eligible to replace the values for scheduled visits), the baseline Hb value will be averaged over the available data.

Baseline for FACIT-Fatigue is defined as the mean of the assessment performed at Screening Visit 1 and Day 1. For patients where data are missing for either Screening Visit 1 or Day 1, the data from the other visit will be used as baseline. If data for both visits are missing, then it will be considered missing and will not be imputed. Patients with baseline value missing will not be included in the analysis.

Baseline for all other objectives is defined as Day 1 or, in case of missing data on Day 1, any previous assessment done during Screening. In case multiple assessments during screening are available, the most recent assessment should be used.

More details are provided in Table 5-2 in the Appendix.

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

2.1.1.5 On-treatment period, study treatment period and follow-up period

The **on-treatment period** of LNP023 lasts from the date of first administration of study treatment to the date of the last actual administration of LNP023 plus 7 days.

This on-treatment period is the reference period for Treatment Emergent Adverse Events (TEAE).

The **study treatment period** is defined as the date of the first administration of the investigational treatment (inclusive) to the last administration, the participant's death date or the date of last contact (in case the participant is lost to follow-up), whichever occurs first. For participants continuing treatment in REP, the study treatment period ends with the last administration during the CLNP023C12303 study.

The duration of **follow-up** starts at Day 1 (inclusive) and lasts to the end of study disposition date, or the participant's death, or date of last contact in case of lost to follow-up or date of the last follow-up visit after early treatment discontinuation (ETD), whichever occurs first.

The study treatment period and duration of follow-up will be summarized by descriptive statistics.

2.1.1.6 Unscheduled visits

The term **unscheduled visit** refers to visits that are not planned and not defined in the SoA in the CTP. In general, data collected at unscheduled visits will not be used in by-visit tabulations or graphs unless the measurements fall within the time window of a scheduled visit (which fit the criteria for visit mapping and the time window of the scheduled visits defined in Table 1-1 in the study protocol shall be used). However, they will be included in analyses of safety parameters based on all post-baseline values such as summary statistics of clinically notable

abnormalities of laboratory data. All data collected at both scheduled and unscheduled visits will be included in data listings.

2.1.1.7 Date of last contact

The **date of last contact** will be derived using the latest complete date among the following:

- All assessment dates.
- Medication start and stop dates if not imputed, including study medication, concomitant medication, and therapies administered after study treatment discontinuation.
- Adverse events start and stop dates if not imputed.
- Last contact date collected if appropriate in the eCRF.
- Withdrawal of consent (in case of withdrawal from study).
- Participant's death.

2.2 Analysis sets

The **Screening Set (SCR)** consists of all participants who have been screened. If a participant has been screened a second time, then the participant should be included for his/her second screening.

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.

2.2.1 Subgroup of interest

Subgroup analyses will be performed for the primary and key secondary endpoint to explore the consistency of treatment effects between subgroups and the overall study population. Results may be graphically presented, e.g., as forest plots.

- Length of time since diagnosis (<2years, ≥2 years)
- Age categories (<45 years, ≥ 45 years)
- Sex (male, female)
- Baseline Hb levels (<12 g/dL, ≥ 12 g/dL)
- Geographical region (US and other countries)

Additional subgroups may be defined later. All subgroup analyses are exploratory.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number of participants in each analysis set will be presented.

Based on the SCR, the number and percentage of participants who are screened, screened but not treated will be presented by reasons for screen failure, derived from the Disposition and/or Inclusion/Exclusion Criteria CRF. For subjects screened twice, the data from the second screening visit will be used in summaries.

Based on the FAS, the number and percentage of participants who completed treatment/who discontinued the treatment will be summarized. The primary reason for treatment discontinuation will be presented.

Based on the FAS, the number of participants enrolled by region (US, Europe and other) and by country will be presented.

For the FAS, number of participants with important protocol deviations will be tabulated by deviation category and deviation. Participants with multiple protocol deviations in a category will only be counted once at each level of summarization. Participants with protocol deviations related to COVID-19 will be summarized as well.

2.3.2 Demographics and other baseline characteristics

Demographics 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 for continuous data will be mean, standard deviation (SD), median, 25^{th} and 75^{th} percentiles, minimum, and maximum.

2.3.3 Relevant medical histories and current medical conditions

The following summaries will be presented for the FAS.

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 treatment period. Relevant medical history terms and current medical conditions at baseline (started before screening 1 and on-going during screening) separately by system organ class (SOC) and preferred term (PT) will be summarized. A listing of medical history will be provided.

PNH history will be reported based on the 'PNH History' CRF. Specifically, the PNH disease duration derived from the start date up to the date of screening will be summarized.

History of aplastic anemia will be reported by absolute number and proportion. Patients who do not receive treatment during the study but had aplastic anemia prior to informed consent date and patients who receive treatment but had aplastic anemia prior to Day 1 will be considered as presence of history of aplastic anemia.

History of MAVE (MAVEs prior to screening) will be summarized based on the 'MAVE History' CRF by medical history term.

Vaccination history will be presented by serogroup/polyvalent type.

PNH related signs and symptoms at baseline will be tabulated.

CCI [redacted]

Anti-C5 treatment history will be presented based on the 'Anti-C5 medication prior to and during screening' CRF reporting the type of medication (eculizumab or ravulizumab), time from start date to last dose prior to Day 1, and the treatment regimen (dose and frequency).

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).

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

2.4.1 Study treatment / compliance

The SAF will be used for all analyses described below.

The **duration of exposure** to iptacopan will be computed and summarized as the duration of the treatment, but excluding temporary treatment interruptions (expressed as: Duration of exposure=Date of last known study drug-Date of first dose of study drug+1 excluding temporary treatment interruptions). The minimal duration of interruption defined for exclusion of the duration of exposure is one full day without any dose. Since iptacopan is administered twice a day, only days with zero dose will be considered as an interruption.

The duration of exposure will be the basis for the computation of the dose intensity and relative dose intensity. The **dose intensity** (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the **relative dose intensity** (computed as the ratio of dose intensity and planned dose intensity so that for a participant receiving all doses as planned it is equal to one) will be summarized by means of descriptive statistics. In addition, dose intensity categories (<400 mg/day, 400 mg/day and >400 mg/day) and relative dose intensity categories (≤75%, >75 to 90%, >90 to 100%, >100%) will be displayed. The planned dose intensity is 200 mg b.i.d. (corresponding 400 mg/day of iptacopan) administered for 24 weeks without any change in dose or treatment interruptions.

In case there are any study treatment interruptions in the study, the number of participants with interruptions, number of interruptions and durations of interruptions will be summarized. The information on study medication intake for participants having at least one interruption will be listed. In addition, the number of participants with missed doses (defined as missing one capsule of iptacopan 200 mg per day) and number of missed doses will be summarized. The primary reason for dose changes such as missed doses will also be summarized based on the 'Study Treatment LNP023' CRF ('subject decision' vs. other reason).

The **duration of the treatment** will be computed as the time from the date of first study treatment administration to the date of the last actual administration of study treatment (any dose). Descriptive statistics of the treatment duration (in weeks) will be provided. The time to

study treatment discontinuation (end of study treatment as defined in Section 2.1.1.5) may be graphically presented (e.g., by a Kaplan-Meier curve and/or waterfall plot).

Additionally, the frequency and percentage of participants will be provided by **cumulative treatment duration**:

- ≥4 weeks
- ≥8 weeks
- ≥12 weeks
- ≥16 weeks
- ≥20 weeks
- ≥24 weeks

The **overall participant-years on treatment** will be computed and summarized based on the duration of study treatment (in days) as follows:

Overall participant-years= $\sum_{i=1}^{n} study\ treatment\ duration_i\ /365.25$

for i = 1, 2,…, n participants, where n is the total number of participants in the SAF.

2.4.2 Prior, concomitant and post therapies

Analyses in this section will be based on the SAF.

Prior therapies are defined as any medications and significant non-drug therapies administered and terminated at least one day prior to Day 1.

Concomitant therapies are defined as any medications and significant non-drug therapies administered during the duration of the study treatment period as defined in Section 2.1.1.5, i.e., end date on or after Day 1, ongoing at EOS, or with start date prior to end of study treatment and missing end date. It does **not** include the 7-day window after the last dose of iptacopan as in the definition of the on-treatment period for treatment emergent adverse events (TEAE); such therapies should be reported as post-treatment therapies.

Post-treatment therapies are defined as any medications and significant non-drug therapies started after ETD.

Prior, concomitant, and post-treatment therapies will be listed and summarized based on the latest version of the coding dictionary (MedDRA/NovDTD based on WHO Drug Dictionary Enhanced). Among the concomitant medications, rescue medications will be summarized based on SAF. Medications will be presented in alphabetic order according to the Anatomical Therapeutic Chemical (ATC) classification system and by preferred term. Significant prior and concomitant non-drug therapies and procedures will be summarized by primary system organ class and preferred term. Prior, concomitant, and post-treatment therapies will be recorded and summarized separately for surgical and medical procedures. Tables will show the number and percentage of participants receiving at least one drug of a particular preferred term and at least one drug in a particular ATC class.

A categorical summary of participants' vaccination history and vaccinations during study (as captured by the corresponding CRFs) will be provided by vaccine serogroup/polyvalent type. All vaccinations will also be recorded as prior and/or concomitant medication, as appropriate.

2.5 Analysis supporting primary objective(s)

2.5.1 Primary endpoint: change from baseline in Hb levels tested for non-inferiority

The primary endpoint is the change from baseline in Hb levels, where baseline is defined in Section 2.1.1.3 and the post-baseline level of interest is the mean of Hb levels assessed at Day 126, Day 140, Day 154, and Day 168.

The estimation of change from baseline in Hb levels will be handled by the hypothetical strategy where participants are assumed as if they would not have received RBC transfusions while on treatment (RBC transfusions are expected to be rare).

2.5.2 Statistical hypothesis, model, and method of analysis

The primary objective is to assess the efficacy of iptacopan after 24 weeks of treatment in PNH patients who have Hb ≥10 g/dL in response to prior SoC treatment with eculizumab or ravulizumab and switch to iptacopan by demonstrating **non-inferiority** to -1 g/dL in change from baseline in Hb levels between Day 126 and Day 168.

Assuming that patients have stable Hb levels at study entry, the mean change from baseline in Hb level between Day 126 and Day 168 is expected to be unchanged should patients have continued on anti-C5 treatment. Non-inferiority of iptacopan will therefore be tested by the null hypothesis (H_0) against the alternate hypothesis (H_1) comparing the mean change from baseline in Hb level in iptacopan between Day 126 and Day 168 (μ) to -1 g/dL:

H_0: $\mu <= -1$

H_1: $\mu > -1$

Hypothesis testing for the primary objective is a one-sided test with nominal significance level of 0.025. Non-inferiority will be concluded, and primary objective will be considered met if the lower bound of the estimated two-sided 95% confidence interval (CI) is greater than -1 g/dL.

The primary analysis of the primary endpoint will be performed using a mixed model for repeated measures (MMRM) considering an unstructured covariance matrix. All visits will be included in the analysis. The model will include age, sex, visit, baseline Hb levels and the interaction between visits and baseline Hb levels. The MMRM will estimate the treatment effect as the average change from baseline to the study visits occurring between Day 126 and Day 168. In case of non-convergence issues, the Autoregressive (AR(1)) covariance structure will be employed in the first instance; further steps in case issues persist are described in Section 5.2.2 in the Appendix.

The imputation strategies for missing data due to intercurrent events or missing data unrelated to intercurrent events are described in Section 2.5.4 and Section 2.5.5. 100 imputed datasets

will be created. Each imputed dataset will be analyzed, and results will be combined using Rubin's rule.

2.5.3 Justification of the non-inferiority margin

The non-inferiority margin is proposed based on clinical data and experience as well as on precedence with Hb stabilization as endpoints. In the 301 study (Lee et al 2019) and 302 study (Kulasekararaj et al 2019) with ravulizumab, Hb stabilization is defined as the avoidance of a ≥2 g/dL decrease in Hb level from baseline in the absence of transfusion, while in the Phase 3 PRINCE study with pegcetacoplan, a more conservative cutoff value of -1 g/dL was used (Wong et al 2021). Hence a decrease of less than 1 g/dL in Hb level from baseline at Day 168 does not indicate a decline in hematological response. Moreover, the data from the study CLNP023C12301 indicates that the SD (inter-subject variability) of change from baseline in Hb levels between Day 126 and Day 168 is around 1.5 g/dL. This indicates that the NI margin of -1 g/dL is within natural variability and is sufficient to demonstrate non-inferiority in Hb levels after treatment switch to iptacopan vs baseline (anti-C5).

2.5.4 Handling of intercurrent events

Treatment policy

Intercurrent events stemming from treatment discontinuation for any reason, BTH events, and MAVEs will be handled with a treatment policy. Missing Hb data after treatment discontinuation will be imputed based on a "back to pre-treatment level" approach. This will be implemented by imputing missing values from a normal distribution with mean and standard deviation derived from participants' baseline Hb values (as defined in Section 2.1.1.3). This approach aims to be consistent with the inclusion of hemoglobin data under the treatment policy strategy following all other intercurrent events. For patients who have early treatment discontinuation (ETD) but remain in the study, the observed data collected after ETD but before EoS will be used for analysis.

Hypothetical strategy

RBC transfusions will be handled using a hypothetical strategy. Hb values obtained during 30 days after RBC transfusion will be excluded and imputed as if participant would not have received the transfusion on iptacopan treatment.

The imputation will be performed under the missing at random (MAR) assumption based on Hb levels (continuous variable) for measurement during the treatment period. More details are provided in the Appendix in Section 5.2.2

In case of treatment discontinuation, hemoglobin levels at visits during 30 days after the transfusion **and only until** treatment discontinuation will be imputed under the MAR assumption as described above. The imputation of Hb values during 30 days after the transfusion and **after** treatment discontinuation will be imputed based on a "back to pre-treatment level" approach.

In case a participant receives RBC transfusions over consecutive days (N=number of days), Hb values obtained during 30+N-1 days after the first RBC transfusion will be excluded and imputed as described above.

More details on the imputation strategy are provided in the Appendix in Section 5.2.2.

2.5.5 Handling of missing values not related to intercurrent events

Missing Hb data after early study discontinuation will be imputed based on a "back to pre-treatment level" approach.

For participants with intermittent missing data during the study where reasons for missingness are assumed to be unrelated to response or compliance status, the missing data will be handled under the MAR assumption based on Hb levels (continuous variable). More details are provided in the Appendix in Section 5.2.2.

2.5.6 Sensitivity analyses

A sensitivity analyses will be performed where missing central lab Hb data will be replaced by available local lab data collected at the same visit. The same analysis model as for the main analysis will be used.

2.5.7 Supplementary analyses

The following supplementary estimands will be considered:

- The same analysis as the main analysis will be performed but where all intercurrent events will be handled using a treatment policy.

In case there will be any pregnancy during the study, the following supplementary estimand will also be considered:

- The same analysis as the main analysis will be performed but where treatment discontinuation **due to pregnancy** will be handled using a hypothetical strategy as if the patient had continued on the study. Hb data after treatment discontinuation due to pregnancy will be imputed under the MAR assumption. Treatment discontinuation for any **other reason** will be handled using a treatment policy. Missing Hb data unrelated to response or compliance will be handled under MAR assumption. Missing data after treatment discontinuation not related to pregnancy will be imputed using a "return to pre-treatment level" approach.

2.5.8 Supplementary graphics and descriptive statistics

The least squares mean estimate of the changes from baseline and the associated 95% CI will be plotted over time (study visits).

The following descriptive statistics and graphics supporting the primary objective will be based on non-imputed, observed data. Descriptive statistics for the components of the primary endpoint will be presented: summary statistics on baseline Hb values and post-baseline Hb value of interest, number of BTH events, MAVE events and RBC transfusions, and number of participants having no missing Hb data in the in last six weeks (from Day 126 to Day 168). In

addition, the occurrence of BTH events, MAVE events and RBC transfusions (this will be reported for patients who meet the criteria of transfusion and for patients who actually receive transfusion) may be graphically presented (e.g., as swimmer plots), if applicable.

The occurrence of missing Hb values and the occurrence of local lab Hb assessments where central lab Hb assessments are missing will be graphically presented (e.g., as heat maps). In addition, the distribution of Hb data (central lab vs. local lab) may be graphically presented.

The observed Hb values will be summarized over time (study visits). In case there will be any RBC transfusions during the study, the same summary statistics will be prepared but considering Hb assessments 30 days after transfusions as missing (if applicable given that few RBC transfusions are expected).

In addition, a graph (e.g., spaghetti plot) showing the trend of Hb values from prior to screening (historical data) to screening and then over the treatment period will be provided.

2.6 Analysis supporting secondary objectives

2.6.1 Secondary endpoints

2.6.1.1 Key secondary analysis: change from baseline in Hb levels tested for superiority

The key secondary objective is to assess efficacy of iptacopan after 24 weeks of treatment in PNH patients who have Hb ≥10 g/dL in response to SoC and switch to iptacopan by demonstrating **superiority** in change from baseline in Hb levels between Day 126 and Day 168.

Based on the justification provided below, superiority will be tested by the null hypothesis (H_0) against alternative hypothesis (H_1) comparing the mean change from baseline in Hb level in iptacopan between Day 126 and Day 168 (μ) to 0:

$H_0: \mu \leq 0$

$H_1: \mu > 0$

Hypothesis testing for the key secondary objective is a one-sided test with nominal significance level of 0.025. The statistical model for the key secondary endpoint is the same as for the primary analysis. Superiority will be concluded and the key secondary objective will be considered met if the lower bound of the estimated two-sided 95% CI is greater than 0 g/dL. The overall study Type I error is one-sided 0.025.

Justification of the superiority test

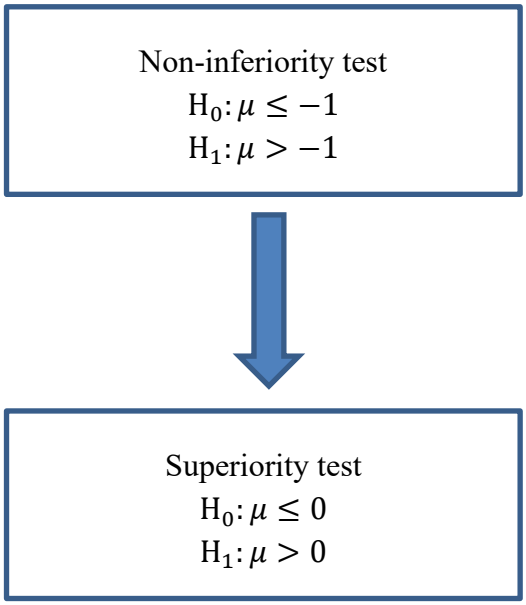
The Ultomiris CHMP Assessment Report (EMA 2019) indicates that change from baseline in Hb levels at Day 168 is close to zero for PNH patients who received anti-C5 treatment. Suppose PNH patients continue anti-C5 treatment without switching to iptacopan, the mean Hb levels at Day 168 should be close to the mean Hb levels at baseline. Data from the PEGASUS study (Hillmen et al 2021) show that the least squares mean change from baseline in Hb was 2.37 g/dL with pegcetacoplan and -1.47 g/dL with eculizumab, indicating that patients of treatment with eculizumab may also worsen after 4 months of treatment. The results of a supportive

analysis of the primary endpoint that included all available data (not censored for transfusions) showed that the adjusted mean change from baseline to Week 16 was 2.66 g/dL with pegcetacoplan and −0.03 g/dL with eculizumab indicating that the population of patients treated with eculizumab remained stable with the support of RBC transfusion. In the eculizumab group, patients with fewer than four transfusions in the 12 months before screening had a decrease in Hb of 0.01 g/dL**.** This indicated that the margin of 0 g/dL is an acceptable one to declare superiority of iptacopan over eculizumab/ravulizumab treatment.

2.6.1.2 Multiplicity adjustment

The non-inferiority test of iptacopan on the primary endpoint and the superiority test of iptacopan will be tested hierarchically (Figure 2-1). Multiplicity adjustment is not needed.

Figure 2-1 Hierarchy of testing non-inferiority and superiority of iptacopan



2.6.1.3 Proportion of participants achieving sustained Hb levels ≥ 12 g/dL in the absence of RBC transfusions

The proportion of participants achieving sustained Hb levels ≥12 g/dL on three out of four measurements assessed between Day 126 and Day 168 in the absence of RBC transfusions between Day 1 and Day 168 will be evaluated by observed proportions. The proportion of responders will be the mean of proportion of responders from all the imputed dataset, and the 95% CIs will be derived by the bootstrap method (as described in Section 5.2.3 in the Appendix).

2.6.1.4 Transfusion avoidance between Day 1 and Day 168

Transfusion avoidance will be evaluated as the proportion of participants not requiring any transfusion between Day 1 and Day 168, i.e., not received and not met the criteria for RBC administration, which are defined as follows:

- Hb ≤ 9 g/dL with signs and/or symptoms of sufficient severity to warrant a transfusion
- Hb ≤ 7 g/dL, regardless of presence of clinical signs and/or symptoms

Note that the above calculation will be based on observed data (observed transfusion as captured in the CRF) rather than imputed datasets. The 95% confidence interval will be calculated using Wilson's methods.

The number and percentage of participants not receiving and not meeting the criteria for administration of packed RBC transfusions during the treatment period will be summarized overall and by transfusion history during 12-6 months prior to screening (i.e., transfusion received vs. not received).

If any participant will receive/require any RBC transfusion, the time to first packed RBC transfusion/meeting one of the criteria above will be plotted using Kaplan-Meier curves. In addition, the number of RBC transfusions (required/received) will be summarized and graphically presented (e.g., as swimmer plots if there is sufficient number of events). In addition, the units of RBC transfusions, the Hb 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.

2.6.1.5 Change from baseline in ARC

The estimation of the change from baseline in ARC will be derived from an MMRM using data from all visits. The model will include age, sex, visit, baseline ARC and the interaction between visits and baseline ARC. An unstructured covariance matrix will be used. The MMRM will estimate the average change from baseline to the study visits occurring between Day 126 and Day 168 (similarly as described for the primary analysis). The MMRM will be performed for each imputed datasets and these results will be combined using Rubin's rule. The least squares mean estimate of the changes from baseline and the associated 95% CI will be plotted over time (study visits).

In addition, the observed ARC values at each study visit will be summarized.

2.6.1.6 Percent change from baseline in LDH

The treatment effect on percent change from baseline in LDH will be assessed using an MMRM of the log-transformed ratio to baseline using data from all visits. The model will include age, sex, visit, log-transformed baseline LDH and the interaction between visits and log-transformed baseline LDH. An unstructured covariance matrix will be used. The treatment effect will be derived based on the average of the log-transformed ratio to baseline estimated from the study visits occurring between Day 126 and Day 168 (back-transformed geometric mean). The MMRM will be performed for each imputed datasets and these results will be combined using Rubin's rule. The estimated ratio to baseline and associated 95% confidence intervals will be presented over time (study visit).

In addition, the observed LDH values and observed ratio to baseline values at each study visit will be summarized.

2.6.1.7 Difference in TSQM-9 scores between Day 1 and Day 84/Day 168

The TSQM-9 scores at each study visit will be derived as described in the Appendix. The results at each study visit will be presented separately for the three TSQM-9 domains (effectiveness, convenience, and global satisfaction). Descriptive summaries and graphics (e.g., boxplots) will be provided. The treatment effect on change from baseline in domain score will be assessed using an MMRM. The model will include age, sex and visit. An unstructured covariance matrix will be used.

In addition, the number/frequency of responses to each of the questions across the three TSQM-9 domains and at each study visit will be summarized.

2.6.1.8 Change from baseline in FACIT-Fatigue scores at Day 84 and Day 168

Test scores from all visits will be included in this analysis where baseline is defined as the mean of the test results at the Screening Visit 1 and Day 1 (Section 2.1.1.3). The analysis will be performed using an MMRM considering an unstructured covariance matrix. The model will include age, sex, baseline score, study visit and the interaction between visits and baseline score. The MMRM will estimate the average change from baseline to the study visits at Day 84 and Day 168. The least squares mean estimate of the changes from baseline and the associated 95% CI will be plotted over time (study visits).

In addition, the observed FACIT-Fatigue scores at each study visit will be summarized.

2.6.1.9 Rates of BTH and MAVE between Day 1 and Day 168

The information on BTH 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 AE summaries. The number and percentage of participants experiencing clinical BTH will be summarized. The information on whether the participant received packed RBC transfusions and the quantity of packed RBC transfusion due to clinical BTH will be summarized. Clinical BTH events (including those in the screening period) will be listed and the treatment emergent events will be flagged.

Similarly, the 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 AE summaries. The number and percentage of participants with MAVEs 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.

The estimation of rates of BTH and MAVE will be carried out using a negative binomial model. No covariates are planned to be included. If the negative binomial model fails to converge or to give valid estimates, the Wilson method will be applied (Miettinen and Nurminen 1985).

2.6.2 Handling of intercurrent events

All intercurrent events will be handled using treatment policy except for RBC transfusions for the secondary endpoint of achieving sustained Hb levels ≥ 12 g/dL (Section 2.6.1.2). In this

case, RBC transfusions are part of the composite endpoint and will qualify the participant as a non-responder.

2.6.3 Handling of missing values not related to intercurrent events

Missing data not related to intercurrent events will be handled following the same principles as described for the primary objective (Section 2.5.5) except for the FACIT-Fatigue and TSQM-9 analysis, where a complete case analysis will be performed. The imputed values for hemoglobin will be used to derive whether patients met the secondary endpoint of achieving sustained Hb levels ≥ 12 g/dL in the absence of transfusion between Day 1 and Day 168. However, the imputed Hb values will not make patients qualify for meeting "transfusion criteria".

2.6.4 Sensitivity analyses

As for the primary estimand, sensitivity analyses will be performed where missing central lab data will be replaced by available local lab data collected at the same visit. Such a sensitivity analysis will be performed for the key secondary estimand (Section 2.6.1.1), the proportion of participants achieving sustained Hb levels ≥ 12 g/dL in the absence of RBC transfusions (Section 2.6.1.3), ARC (Section 2.6.1.5) and LDH (Section 2.6.1.6). For an overview of sensitivity analyses, see also Table 5-1 in the Appendix.

2.6.5 Supplementary analyses

The same supplementary analyses as described for the primary endpoint/objective will be considered for the key secondary endpoint/objective (Section 2.5.7).

For the secondary endpoints of change from baseline in ARC and LDH, a supplementary analysis will be performed where RBC transfusion will be handled using a hypothetical strategy instead of a treatment policy (see Table 5-1 in the Appendix).

2.7 Safety analyses

The analysis set used for all safety analyses will be the SAF.

For analyses based on the SAF, different baseline values need to be considered as described in Section 2.1.1.3.

Safety summaries (tables, figures) include only data from the on-treatment period except for baseline data which will also be summarized where appropriate (e.g., change from baseline summaries). Summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs) as defined in Section 2.1.1.5. In addition, a separate summary of death events including on-treatment and post-treatment deaths will be provided, if applicable.

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 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 [PT]) and treatment-emergent serious AEs (SAEs) will be summarized in the following ways:

- by primary system organ class (SOC) and PT.
- by primary SOC, PT, and maximum severity.
- Separate summaries will be provided for AEs reported as suspected to be related to study medication, deaths, SAEs, AEs leading to discontinuation of study medication and AEs of special interest.

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

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

To address the issue of variable on-treatment duration within the study, the exposure-adjusted occurrence rate of treatment-emergent AEs will be presented by primary SOC and PT.

For the most common AEs (at least 5% of participants for each PT), the 95% CI of the exposure-adjusted occurrence rate of treatment-emergent AEs can be presented.

Exposure-adjusted occurrence 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 the sum of the duration of on-treatment periods over patients (in days) divided by 365.25. The approximate 95% CIs for the occurrence rate will be calculated as described in the program-level SAP (Master Analysis Plan [MAP]) with correction for overdispersion using the asymptotically robust method (Scosyrev 2016, Scosyrev and Pethe 2022).

This method will account for the length of the on-treatment duration 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 uses by default the on-treatment period which includes periods of treatment interruption during which there is no exposure. This is considered as adequate when interruptions are accidental (for instance temporary interruptions for safety reasons or doses accidentally missed).

2.7.1.1 Adverse events of special interest

Adverse events of special interest (AESI) are defined in the latest version of the compound electronic Case Retrieval Strategy (eCRS) from the Signal Detection & Management System (SDMS) tool. 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 safety topics of interest. Safety topics of interest to be reported are identified by the flag "SPPFL"="Y".

The number (and percentage) of participants with treatment-emergent AEs of special interest 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 PT. The exposure adjusted incidence rates and associated 95% CI (as described in Section 2.7.1) will be presented for each safety topic of interest/AEs/SAEs.

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

2.7.1.2 Adverse events reporting for safety disclosure

For the legal requirements of clinicaltrials.gov and EudraCT, two required tables on treatment-emergent AEs which are not serious AEs with an incidence greater than 5% and on treatment-emergent AEs events and SAEs suspected to be related to study treatment, will be provided by SOC and PT for the SAF.

In case a participant experiences several consecutive AEs (irrespective of study treatment causality, seriousness, and severity) 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 AEs 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 treatment-emergent AEs will be summarized by system organ class and preferred term. Death refers to treatment-emergent adverse events with fatal outcome. In addition, a separate summary of death evnts including on treatment and post treatment deaths will be provided.

All 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 (hematology, clinical chemistry, urinalysis/urine dipstick assessments, coagulation/markers of thrombosis).

For all continuous laboratory parameters, the absolute on-treatment laboratory values (as defined in Section 2.1.1.5) will be summarized with standard descriptive statistics (mean, median, standard deviation, minimum, maximum) by parameter, and scheduled visit/time point.

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

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

- Values less than the 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 figures, imputed values will be displayed.

Shift tables using the Common Terminology Criteria for AEs (CTCAE) grading (latest version 4.03) may be provided as appropriate to compare participant's baseline laboratory evaluation relative to the visit's observed value. These summaries will be presented by laboratory parameter and visit. Shift tables for biochemistry parameters that are not CTCAE graded will also be provided to show patients with a change from normal to abnormal.

Plots of arithmetic mean and SD over time will be provided for all hematology and clinical chemistry parameters. For selected laboratory parameters, abnormalities occurring at any time from scheduled, unscheduled and premature discontinuation visits will be summarized considering all post-baseline on-treatment data. Where normal ranges are available, abnormalities in laboratory data will be listed by participant and visit/time. Moreover, separate listings for hematology, biochemistry and urinalysis will be provided.

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 2-1. 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, International Normalized Ratio (INR) is routinely monitored and can be used for the definition of liver function events.

Table 2-1 Liver toxicities

Definition	Label for output display
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)

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 will be based on eCRS and is described in Table 2-2 for MedDRA version 27.1

Table 2-2 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

HLGT: High Level Group Term

MedDRA codes listed above are based on version 27.1. The list will be updated for each MedDRA version change and will be included in the eCRS with flag "OS". eCRS will be the reference for analyses.
(1) presence of Fatigue term with severity ≥ "Severe"

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 be presented as part of AEs by PT (either in a separate table or as part of the general AE tables).

In addition, the number of patients meeting the following potential drug induced liver injury (DILI) definitions will also be summarized and listed. If a patient met the criteria for more than one category, the patient will only be counted once in the most severe case category, with Hy's law case as the most severe category and cholestasis case the least severe category.

- Hy's Law defined as post-baseline TB elevation to >=2x ULN along with concurrent ALP <2x ULN, occurring on or within 30 days after a post-baseline ALT or AST elevation to >=3x ULN
- Temple's corollary defined as ALT and/or AST >=3x ULN but there is no accompanying TB elevation or jaundice (defined as with non-missing TB reading <2XULN on the same date as ALT/AST)
- Cholestasis defined as Jaundice occurs (TB >=2x ULN) with no or minimal hepatocellular injury (defined as non-missing ALT and AST less than 3x ULN on the same date as TB)

Renal safety monitoring

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+

Abnormal renal event findings must be confirmed after ≥24 hours but ≤ 5 days after first assessment. Causes and possible interventions should be considered.

2.7.4 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:

- Resting heart rate sinus rhythm < 30 or a HR decrease ≥ 25%
- HR > 130 [bpm]
- QRS >120 or increase >25% compared to predose baseline [msec]

- QTcF >500 or increase >60 compared to predose baseline [msec]

For any ECGs with participant safety concerns after baseline, two additional ECGs must be performed to confirm the safety finding.

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.

2.7.5 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) for the on-treatment period will be provided for all vital signs data (weight, temperature, pulse rate, SBP, DBP) by visit/time.

Where ranges are available, abnormalities will be summarized and listed by participant and visit/time. Arithmetic mean and SD of absolute values over time for SBP and DBP 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 BO: 65-95 mmHg
- Heart rate:
  1. <=50 bpm
  2. >=120 bpm
- Temperature > 38.3 °C (>101°F)

2.8 CCI

[redacted]

CCI

2.9 CCI

2.10 Patient-reported outcomes (PRO)

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, and satisfaction as measured by the TSQM-9. These analyses are secondary endpoints described in Section 2.6.1.7 and Section 2.6.1.8.

CCI

2.11 CCI

CCI

2.12 CCI

2.13 CCI

- CCI [redacted]

[redacted]

2.14 Interim analysis

If deemed required (e.g., to support regulatory submissions to Health Authorities), interim safety analyses may be produced while the study is still ongoing. These safety analyses will be provided upon request and will be described in a separate analysis plan.

3 Sample size calculation

3.1 Primary endpoint

For a sample size of 50 participants, the power for testing against a NI margin of -1 g/dL would be more than 94% based on the assumption that the true mean change from baseline in Hb levels as mean of visits between Day 126 and Day 168 is more than 0 g/dL with a SD of 2.0 g/dL.

Table 3-1 Power for non-inferiority test based on different assumptions

True mean change from baseline in Hb (g/dL)	Standard deviation (g/dL)	Power
0.8	2.0	>99%
0.8	1.5	>99%
0.2	2.0	99%
0.2	1.5	>99%
0.0	2.0	94%
0.0	1.5	>99%
-0.2	2.0	81%
-0.2	1.5	96%
-0.6	2.0	29%
-0.6	1.5	47%

3.2 Key secondary endpoint

For a sample size of 50 participants, the power for testing against superiority would be 94% based on the same assumption the true mean change from baseline in Hb levels as mean of visits between Day 126 and Day 168 is 1.0 g/dL with a SD of 2.0 g/dL.

Table 3-2 Power for superiority test based on different assumptions

True mean change from baseline in Hb levels (g/dL)	Standard deviation (g/dL)	Power
1.5	2.0	>99%
1.5	1.5	>99%
1.2	2.0	99%
1.2	1.5	>99%
1.0	2.0	94%
1.0	1.5	>99%
0.8	2.0	81%
0.8	1.5	96%
0.6	2.0	56%
0.6	1.5	81%

4 Change to protocol-specified analyses

- No logistic regression will be considered for the analysis of the secondary endpoints 2 (composite of having Hb levels ≥ 12 g/dL on three out of four assessments between Day 126 and Day 168 in the absence of RBC transfusions between Day 1 and Day 168) and 3 (transfusion avoidance between Day 1 and Day 168). Only the observed proportions of responders will be reported. The rationale is that a high portion of patients achieving sustained Hb level ≥ 12 g/dL and few events of transfusion is expected.
- Number and units of RBC transfusions were removed from exploratory objectives.

5 Appendix

5.1 Imputation rules

5.1.1 AE end date imputation

Rules for imputing AE end dates are stated below. The date of last contact is defined in Section 2.1.1.7.

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.

5.1.2 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	(a) Before Treatment Start	(b) Before Treatment Start	(b) Before Treatment Start	(b) Before Treatment Start
YYYY = TRTY	(a) Uncertain	(b) Before Treatment Start	(c) Uncertain	(c) After Treatment Start
YYYY > TRTY	(a) After Treatment Start	(b) After Treatment Start	(b) After Treatment Start	(b) After Treatment Start

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

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), 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.

5.1.3 Concomitant medication end date imputation

Rules for imputing the CM end date are stated below. Date of last contact in the study is defined as in Section 2.1.1.7. Concomitant medication end dates will not be imputed for ongoing records.

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.

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).

If CM day/month/year is missing then use the date of last contact + 1 day as the imputed CM end date.

If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.

5.1.4 Concomitant medication start date imputation

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	(a) Before Treatment Start	(b) Before Treatment Start	(b) Before Treatment Start	(b) Before Treatment Start
YYYY = TRTY	(a) Uncertain	(b) Before Treatment Start	(a) Uncertain	(c) After Treatment Start
YYYY > TRTY	(a) After Treatment Start	(b) After Treatment Start	(b) After Treatment Start	(b) After Treatment Start

Rules for CM start date imputation

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 investigational treatment	**BTH events**	**MAVEs**	**RBC transfusions**	
Primary and key secondary estimand						
Primary and key secondary estimand (primary estimand 1 and secondary estimand 1)	Change from baseline in Hb levels assessed between Day 126 and Day 168*	Treatment policy. Missing Hb data unrelated to response or compliance handled under MAR assumption. Missing data after treatment discontinuation will be imputed using a "return to pre-treatment level" approach.	Treatment policy	Treatment policy	Hypothetical strategy: imputed under MAR assumption as if participant would not have received RBC transfusions.	Average change from baseline in Hb and 95% CI
Sensitivity analysis 1.1	Same	Treatment policy. Missing Hb data unrelated to response or compliance **replaced by local lab data** from the same visit. Missing data after treatment discontinuation imputed using a "return to pre-treatment level" approach.	Same	Same	Same	Same
Supplementary analysis 1.1	Same	Same	Same	Same	Treatment policy	Same

Estimand	Endpoint	Handling strategy of intercurrent events				Summary measure
		Discontinuation of investigational treatment	**BTH events**	**MAVEs**	**RBC transfusions**	
Supplementary analysis 1.2	Same	Treatment discontinuation **due to pregnancy** will be handled using a hypothetical strategy: imputed under MAR as if participant would not have discontinued treatment. Treatment discontinuation for any other reason will be handled using a treatment policy.	Same	Same	Same	Same
Secondary estimands						
Secondary estimand 2	Composite of having Hb levels ≥ 12 g/dL on three out of four assessments between Day 126 and Day 168* in the absence of RBC transfusions between Day 1 and Day 168	Treatment policy. Missing Hb data unrelated to response or compliance handled under MAR assumption. Missing data after treatment discontinuation will be imputed using “return to pre-treatment level” approach.	Treatment policy	Treatment policy	Not an intercurrent event (included in the composite estimand)	Proportion of responders
Sensitivity analysis 2.1	Same	Treatment policy. Missing Hb data unrelated to response or compliance **replaced by local lab data** from the same visit.	Same	Same	Same	Same

Estimand	Endpoint	Handling strategy of intercurrent events				Summary measure
		Discontinuation of investigational treatment	**BTH events**	**MAVEs**	**RBC transfusions**	
		Missing data after treatment discontinuation imputed using a "return to pre-treatment level" approach.				
Secondary estimand 3	Transfusion avoidance between Day 1 and Day 168	Treatment policy	Treatment policy	Treatment policy	Not an intercurrent event since this is the endpoint of interest	Proportion of responders
Secondary estimand 4	Change from baseline in ARC assessed between Day 126 and Day 168*	Treatment policy. Missing data unrelated to response or compliance handled under MAR assumption. Missing data after treatment discontinuation imputed using "return to pre-treatment level" approach.	Treatment policy	Treatment policy	Treatment policy	Average change from baseline in ARC
Sensitivity analysis 4.1	Same	Treatment policy. Missing ARC data unrelated to response or compliance **replaced by local lab data** from the same visit. Missing data after treatment discontinuation imputed using a "return to pre-treatment level" approach.	Same	Same	Same	Same

Estimand	Endpoint	Handling strategy of intercurrent events				Summary measure
		Discontinuation of investigational treatment	**BTH events**	**MAVEs**	**RBC transfusions**	
Supplementary analysis 4.1	Same	Same	Same	Same	Hypothetical strategy: imputed under MAR assumption as if participant would not have received RBC transfusions.	Same
Secondary estimand 5	Percent change from baseline in LDH between Day 126 and Day 168*	Treatment policy. Missing data unrelated to response or compliance handled under MAR assumption. Missing data after treatment discontinuation imputed using "return to pre-treatment level" approach.	Treatment policy	Treatment policy	Treatment policy	Average LDH ratio to baseline
Sensitivity analysis 5.1	Same	Treatment policy. Missing LDH data unrelated to response or compliance **replaced by local lab data** from the same visit. Missing data after treatment discontinuation imputed using a "return to pre-treatment level" approach.	Same	Same	Same	Same

Estimand	Endpoint	Handling strategy of intercurrent events				Summary measure
		Discontinuation of investigational treatment	**BTH events**	**MAVEs**	**RBC transfusions**	
Supplementary analysis 5.1	Same	Same	Same	Same	Hypothetical strategy: imputed under MAR assumption as if participant would not have received RBC transfusions.	Same
Secondary estimand 6	Difference in scores of the TSQM-9 domains between baseline and Day 84 and Day 168	Treatment policy. Missing data will not be imputed (complete case analysis).	Treatment policy	Treatment policy	Treatment policy	Mean change from baseline in TSQM-9 scores
Secondary estimand 7	Change from baseline in FACIT-F scores	Treatment policy. Missing data will not be imputed (complete case analysis)	Treatment policy	Treatment policy	Treatment policy	Mean change from baseline in FACIT-F scores
Secondary estimand 8	Rate of BTH events	Treatment policy	Not an intercurrent event since this is the endpoint of interest	Treatment policy	Treatment policy	Rate of occurrence of BTH
Secondary estimand 9	Rate of MAVEs	Treatment policy	Treatment policy	Not an intercurrent event since this is the endpoint of interest	Treatment policy	Rate of occurrence of MAVEs
* The “assessments between Day 126 and Day 168” here means the last four assessments (Visit 108, Visit 109, Visit 110 and EoS visit).						

5.2.2 Missing data handling: change from baseline in Hb

Estimation of change from baseline in hemoglobin levels is under the hypothetical situation in which participants would not have received RBC transfusions on iptacopan treatment. The hemoglobin values 30 days after transfusion will be removed and imputed with a missing at random approach (see description below for intermittent missing data).

For participants who discontinued the treatment, the model implemented will be 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 (Ratitch and O'Kelly 2011).

All imputed datasets will be analyzed using an MMRM and the least square mean estimates and associated 95% CI will be combined using Rubin's rules.

5.2.3 Missing data handling: Proportion of participants achieving sustained Hb levels ≥ 12 g/dL in the absence of RBC transfusions

The same imputation data sets can be used as for the analysis of the change from baseline in Hb. For each imputed dataset, proportion of responders is

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

where Y_i=1 denotes a patients is responder while Y_i=0 denotes a patient is non-responder. Denote the number of imputed dataset to be L and denote θ_j (j=1,…,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. For each bootstrap sample, we obtain the proportion of responders. Then we will have B estimators, denoted to be $\theta_1^{\{b\}}, \theta_2^{\{b\}}, \ldots, \theta_B^{\{b\}}$. 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 10000 bootstrapped parameter estimates (obtained from 100 imputed datasets and 100 bootstrap samples from each imputed dataset) as the confidence interval boundaries.

5.2.4 Missing data handling: change from baseline in ARC and percent change from baseline in LDH

For participants withdrawing from the study after discontinuation of iptacopan, a return to pre-treatment level approach will be implemented similarly as for the primary and key secondary endpoint.

For participants having intermittent missing data, the reasons are assumed to be potentially unrelated to the response or compliance status, and their missing data will be handled with a MAR approach and imputed consequently.

All imputed datasets will be analyzed using an MMRM. The least square mean estimates and the associated 95% CI will be combined using Rubin's rules.

5.2.5 Note on SAS procedure MIANALYZE and Rubin's rule

If for a given visit, no missing values are reported so that no imputation is performed, we expect that all imputations give the same estimate but with different standard error.
As per the Rubin's rule, the estimate should be:

- The pooled mean difference equals:

$$\bar{\theta} = \frac{1}{m}(\sum_{i=1}^{m} \theta_i)$$

Where i=1 to m reflects the i^{th} imputation dataset and the θ_i are the estimates for each of the m imputation datasets. In this case, as all estimates are equal, the average equals the estimate from any of the imputation datasets.

- The pooled squared standard error is the sum of the within (V_W) and between (V_B) imputation variance.

$$V_W = \frac{1}{m}\sum_{i=1}^{m} SE_i^2$$

Where the SE_i are the standard errors obtained for each of the m imputation datasets.

$$V_B = \frac{\sum_{i=1}^{m}(\theta_i - \bar{\theta})^2}{m-1}$$

The degrees of freedom used to compute the 95% CI and p-value based on the T distribution are

$$df = (m-1) * (1 + \frac{1}{r})^2$$

Where r is the relative increase in variance due to imputation computed as

$$r = \frac{(V_B + \frac{V_B}{m})}{V_W}$$

In the situation where all estimates are equal, $V_B = 0$, r = 0 and df = infinity so that the T distribution used to compute 95%CI and p-values becomes a normal distribution.
In this case, the 95% CI and p-values will be computed using a normal distribution with the estimate computed as the average over the estimates obtained across all imputation datasets and the standard error computed as the square root of V_W , i.e. the square root of the average of squared Standard Errors.
Note that the SAS procedure MIANALYZE produces the Standard Error hence the 95% CI and p-values can easily be computed.

5.3 Rule of exclusion criteria of analysis sets

Participants that have not received the study drug will be excluded from the SAF.

There are no protocol deviations which will lead to exclusion of participants from the FAS.

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.

5.4 Rules for flagging variables

Table 5-2 Rules for flagging variables

Timing of measurement	Type of data	Rule
Baseline	All data	Unless otherwise specified (for Hb and FACIT-F, the average of screening and Day 1 assessments will be used as baseline), the last measurement made prior to administration of the first dose of study treatment will be used as baseline. Baseline assessments scheduled for and captured on Day 1 will be considered baseline measurements regardless of the time of assessment. Only the date part will be considered if there is just one assessment on Day 1. If there are multiple assessments on Day 1, then the following rules will apply: 1.If time of assessment exists: • select the last available measurement prior to the reference start date/time (considering the time of assessment). • if no measurement prior to the reference start date/time exists, then select the earliest measurement after the reference start date/time (considering the time of assessment). 2. If time of assessment does not exist: • the measurement from the scheduled assessment will be used.

5.5 Calculation of TSQM-9 scores

The TSQM-9 instrument is an abbreviated questionnaire based on TSQM Version 1.4: TSQM version 1.4 contains four domains (effectiveness, side effects, convenience, and global satisfaction). In the TSQM-9, the side effects domain is not included, resulting in a total of nine instead of 14 items compared to TSQM Version 1.4 (Atkinson et al 2004, Atkinson et al 2005, Bharmal et al 2009). The nine items of the TSQM-9 are summarized in Table 5-3.

Table 5-3 TSQM-9 items

Item	Question	Response
1	How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?	(1) Extremely Dissatisfied (2) Very Dissatisfied (3) Dissatisfied (4) Somewhat Satisfied

Item	Question	Response
		(5) Satisfied (6) Very Satisfied (7) Extremely Satisfied
2	How satisfied or dissatisfied are you with the way the medication relieves your symptoms?	(1) Extremely Dissatisfied (2) Very Dissatisfied (3) Dissatisfied (4) Somewhat Satisfied (5) Satisfied (6) Very Satisfied (7) Extremely Satisfied
3	How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?	(1) Extremely Dissatisfied (2) Very Dissatisfied (3) Dissatisfied (4) Somewhat Satisfied (5) Satisfied (6) Very Satisfied (7) Extremely Satisfied
4	How easy or difficult is it to use the medication in its current form?	(1) Extremely Difficult (2) Very Difficult (3) Difficult (4) Somewhat Easy (5) Easy (6) Very Easy (7) Extremely Easy
5	How easy or difficult is it to plan when you will use the medication each time?	(1) Extremely Difficult (2) Very Difficult (3) Difficult (4) Somewhat Easy (5) Easy (6) Very Easy (7) Extremely Easy
6	How convenient or inconvenient is it to take the medication as instructed?	(1) Extremely Inconvenient (2) Very Inconvenient (3) Inconvenient (4) Somewhat Convenient (5) Convenient (6) Very Convenient (7) Extremely Convenient
7	Overall, how confident are you that taking this medication is a good thing for you?	(1) Not at All Confident (2) A Little Confident (3) Somewhat Confident (4) Very Confident (5) Extremely Confident
8	How certain are you that the good things about your medication outweigh the bad things?	(1) Not at All Certain (2) A Little Certain (3) Somewhat Certain (4) Very Certain (5) Extremely Certain

Item	Question	Response
9	Taking all things into account, how satisfied or dissatisfied are you with this medication?	(1) Extremely Dissatisfied (2) Very Dissatisfied (3) Dissatisfied (4) Somewhat Satisfied (5) Satisfied (6) Very Satisfied (7) Extremely Satisfied

The TSQM-9 scoring algorithm

The TSQM-9 scoring algorithm is described below. If more than one item is missing per domain, the score should not be computed for this domain and considered missing. If only one item is missing per domain, the score should be calculated as defined below; the question mark "?" indicates "if available".

Effectiveness:

Effectiveness score = [(Item 1 + Item 2 + Item 3 - 3) / 18] x 100

If one item is missing:

Effectiveness score = [(Item 1? + Item 2? + Item 3? - 2) / 12] x 100

Convenience:

Convenience score = [(Item 4 + Item 5 + Item 6 - 3) / 18] x 100

If one item is missing:

Convenience score = [(Item 4? + Item 5? + Item 6? - 2) / 12] x 100

Global satisfaction:

Global satisfaction score = [(Item 7 + Item 8 + Item 9 - 3) / 14] x 100

If either Item 7 or Item 8 is missing:

Global satisfaction score = [(Item 7? + Item 8? + Item 9 - 2) / 10] x 100

If Item 9 is missing:

Overall satisfaction score = [(Item 7 + Item 8 - 2) / 8] x 100

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