NOVARTIS

Clinical Development

LNP023

CLNP023L12201 / NCT05086744

An open-label, multi-center, phase 2 basket study to assess efficacy, safety and pharmacokinetics of iptacopan (LNP023) in participants with autoimmune benign hematological disorders

Statistical Analysis Plan (SAP)

Document type:	SAP Documentation
Document status:	Final
Release date:	21-May-2024
Number of pages:	38

Template Version 4.0, Effective from 23-Apr-2021

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
02-Dec-2021	First version		N/A - First version	N/A
11-Nov-2022	Prior to iDBL	V1.1	Added definition of unique prior therapy.	Section 2.3.2.1 Definition of unique prior therapy
			[redacted]	[redacted]
			Added CTCAE statements to safety analysis.	Section 2.7 Safety analysis
			Added notable changes of ECG data and vital sign data.	Section 2.7.4 Other safety data
			Updated summary of biomarker data to geometric mean and arithmetic mean are kept for reference.	Section 2.11 Biomarkers
			Updated Criteria that cause participants to be excluded for PD and safety set.	Section 5.5 Rule of exclusion criteria of analysis sets
10-Sep-2023	Prior to IA2 DBL	V1.2	Added definition of change from baseline.	Section 2.1.1 General definitions
			[redacted]	
			Added disease characteristics.	Section 2.3.2 Demographics and other baseline characteristics
			Updated category of duration of exposure.	Section 2.4.1 Study treatment/compliance
			Added decoded terms from field of medical history.	Section 2.4.2 Prior, concomitant and post therapies

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Updated content in tables for laboratory parameters with/without CTCAE grade. Added analysis on newly occurring liver enzyme abnormalities. Added analysis on drug-induced liver injury (DILI).	2.7.3.2 Data analysis
			Added analysis on ECG alert values.	2.7.4.1 ECG and cardiac imaging data
			[redacted]	[redacted]
20-Apr-2024	Prior to final DBL	V1.3	Added time window to match the individual data to its closest visit.	2.1 Data analysis general information
			[redacted]	[redacted]
			[redacted]	

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AE	Adverse event
AESI	Adverse events of special interest
ATC	Anatomical Therapeutic Classification
b.i.d.	Twice a day
BM	Biomarkers
C3	Complement Component 3
C4	Complement Component 4
CAD	Cold Agglutinin Disease
CRO	Contract research organization
CSR	Clinical Study report
CV	Coefficient of variation
DAT	Direct Antiglobulin Test
ECG	Electrocardiogram
EoS	End of study
[redacted]	[redacted]
IA	Interim Analysis
IRB	Institutional Review Board
ITP	Immune Thrombocytopenia
[redacted]	[redacted]
KDQoL	Kidney Disease Quality of Life questionnaire
LDH	Lactate Dehydrogenase
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Drug Regulatory Affairs
mg	Milligram(s)
PD	Pharmacodynamics
PDS	Programming Datasets Specification
PK	Pharmacokinetics
PoC	Proof of concept
PR	PR interval
[redacted]	[redacted]
PT	Preferred Term
[redacted]	[redacted]
QT	QT interval
QTcF	QT interval corrected by Fridericia's formula
Q1	Lower quartile
Q3	Upper quartile
RAP	Report and Analysis Plan
RBC	Red blood cell(s)
RR	RR interval
SAE	Serious adverse event

SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
sC5b-9	soluble Complement Component 5 fraction "b" linked to Complement Component 9
SD	Standard deviation
SOC	System Organ Class
TFLs	Tables, Figures, Listings
TTP	Thrombotic Thrombocytopenic Purpura
ULN	Upper limit of normal
ULOQ	Upper limit of quantification
wAIHA	Warm Autoimmune Hemolytic Anemia

1 Introduction

The Report Analysis Plan (RAP) documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for study "CLNP023L12201".

The Statistical analysis plan (SAP) describes the implementation of the statistical analyses planned in the protocol, including planned interim analyses (see Section 2.10) and the full analysis after the final database lock.

The final study protocol, version v03, 26 Apr 2022 is available at the time of finalization of Statistical Analysis Plan.

1.1 Study design

This is an open-label, single-arm (within each cohort), multi-center, non-confirmatory basket study to assess the efficacy, safety and pharmacokinetics of iptacopan in participants with autoimmune benign hematological disorders. The study is set up as a basket study to allow inclusion of new cohorts (=indications).

The study starts with two initial cohorts/indications and participants will be assigned to the relevant cohort based on their diagnosis:

- Cohort 1: participants diagnosed with primary Immune Thrombocytopenia (ITP)
- Cohort 2: participants diagnosed with primary Cold Agglutinin Disease (CAD)

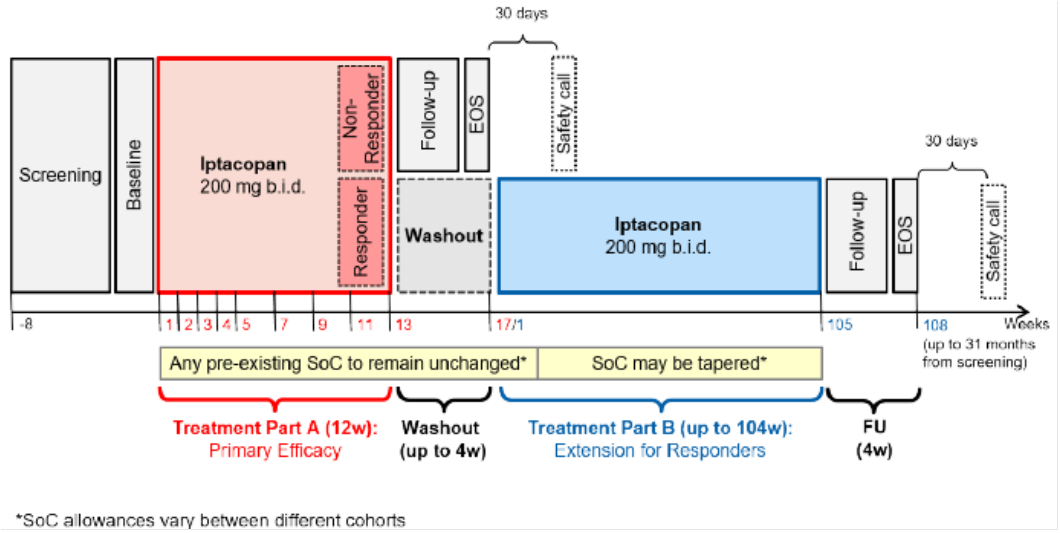
Inclusion of up to two additional cohorts (e.g., Warm Autoimmune Hemolytic Anemia (wAIHA), Thrombotic Thrombocytopenic Purpura (TTP)) will only be proposed via substantial protocol amendment and will only be implemented upon review by HAs/EC/IRBs.

Data analysis will be conducted separately for each cohort. Any analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

Study data will be presented by cohort (ITP, CAD) and, in addition, for ITP, by soluble Complement Component 5 fraction "b" linked to Complement Component 9 (sC5b-9) stratification group (sC5b-9 high, sC5b-9 low).

The study design / participant journey is illustrated in Figure 1-1.

Figure 1-1 Study design



The study consists of a screening period, a 12-week treatment period (Part A), a washout (responders)/follow-up (non-responders) after Part A, and, for responders only, an additional treatment extension period of up to 24 months (Part B). The total study duration from screening until end-of-study visit (EOS) is approximately 6 months for participants not meeting the primary endpoint (non-responders) and up to 31 months for participants meeting the primary endpoint (responders).

1.2 Study objectives, endpoints and estimands

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• **Cohort 1**: To assess the ability of iptacopan to induce a clinically meaningful increase in platelet count in participants with primary ITP	• A clinically meaningful response, defined by a platelet count of ≥50 k/μL sustained for at least 2 consecutive weeks during the main, 12-week treatment part without the use of rescue therapy
• **Cohort 2**: To assess the ability of iptacopan to induce a clinically meaningful increase in hemoglobin levels in participants with primary CAD	• A clinically meaningful response, defined by a hemoglobin level increase of ≥1.5 g/dL above baseline sustained for at least 2 consecutive weeks during the main, 12-week treatment part without the use of rescue therapy
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the time to first response	• **Cohort 1:** Time to first platelet count ≥50 k/μL • **Cohort 2:** Time to first hemoglobin level ≥1.5 g/dL above baseline
• To assess the duration of response during Part A	• **Cohort 1:** Duration during which platelet count remains ≥50k/μL without the use of rescue therapy

Objective(s)	Endpoint(s)
	• **Cohort 2:** Duration during which hemoglobin level remains ≥1.5 g/dL above baseline without the use of rescue therapy
• To assess the magnitude of response during Part A	• **Cohort 1:** Magnitude of platelet count increase from baseline • **Cohort 2:** Magnitude of hemoglobin increase from baseline
• To assess the need for rescue therapy during Part A	• Use of rescue therapy
• **Cohort 2 only**: To assess the effect of iptacopan on relevant disease biomarkers (BM) not covered in the primary objective during Part A	• Lactate dehydrogenase (LDH), total bilirubin, reticulocyte count and haptoglobin
• To assess the safety and tolerability of iptacopan in participants with benign hematological disorders	• Safety parameters include vital signs, adverse events, hematology, blood chemistry, reproductive and thyroid hormones, coagulation, urinalysis and ECG evaluation.
• To assess the pharmacokinetics (PK) of iptacopan	• Iptacopan PK parameters including but not limited to Cmax, AUCtau, AUClast, Ctrough and Tmax.

1.2.1 Primary estimand(s)

The primary clinical question of interest is: What is the effect of iptacopan treatment for 12 weeks on the platelet count in patients with primary ITP and on the hemoglobin level in patients with primary CAD considering the use of rescue medication as an indicator of lack of efficacy.

The justification for targeting this treatment effect is to estimate the effect of the study drug for the full duration in the absence of concomitant treatments that could confound the primary assessment of efficacy.

Cohort 1: primary ITP

The primary estimand is described by the following attributes:

1. Population: Adult participants diagnosed with primary ITP with sustained thrombocytopenia after at least 1 prior line of ITP-directed therapy.
2. Primary variable: Response, where the response is defined as a platelet count of ≥50 k/µL sustained for at least 2 consecutive weeks during the main, 12-week treatment part, a) in the absence of rescue therapy or prohibited medications to treat ITP and b) without study drug discontinuation.
3. Treatment of interest: Investigational treatment with iptacopan 200 mg b.i.d.
4. The summary measure: Proportion of participants who respond.

Cohort 2: primary CAD

The primary estimand is described by the following attributes:

1. Population: Adult participants diagnosed with primary CAD with sustained anemia and laboratory evidence of ongoing hemolysis after at least 1 prior line of CAD-directed therapy.
2. Primary variable: Response, where the response is defined as a hemoglobin level increase of ≥1.5 g/dL above baseline sustained for at least 2 consecutive weeks during the main, 12-week treatment part, a) in the absence of rescue therapy or prohibited medications to treat CAD and b) without study drug discontinuation.
3. Treatment of interest: Investigational treatment with iptacopan 200 mg b.i.d.
4. The summary measure: Proportion of participants who respond.

1.2.2 Secondary estimand(s)

Not applicable.

2 Statistical methods

2.1 Data analysis general information

Data will be analyzed using SAS® version 9.4 (or higher).

Unless otherwise specified, descriptive summary statistics for continuous variables will include number of non-missing observations (n), mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum, as appropriate, while for categorical variables frequencies and percentages will be reported.

Graphical presentations of individual and summary data will be provided, as applicable.

All data collected at unscheduled visits will not be used in 'by-visit' tabulations or graphs, but they will be included in analyses 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 General definitions

The term ***'study treatment'*** or ***'study drug'*** refers to the Novartis investigational drug, LNP023, dispensed by the investigators during the study.

The term ***'date of first administration of study drug/treatment'*** refers to the date on which the study drug/treatment was given for the first time in each study part.

The term ***'date of last administration of study drug/treatment'*** refers to the date on which the study drug/treatment was given for the last time in each study part.

The term ***'study day'*** refers to the Analysis Relative Day, Relative Start Day or Relative End Day, as applicable. Study Day is defined relative to the Analysis reference date, which is the date of first administration of the study drug/treatment in each study part;

- The study day in each study part for a scheduled or unscheduled visit on or after the Analysis reference date 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 (applicable only for Part A) is defined as:

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

  Thus, the Analysis reference date in each study part will be study day 1. For Part A only, the date directly prior to the Analysis reference date is defined as Study Day -1 (there is no Study Day 0).

For Part A, the term ***'baseline'*** refers to the last measurement before dose administration, unless otherwise specified. For Part B, baseline is defined as study day 1. Exceptionally, for platelets (ITP) / hemoglobin (CAD), 'baseline' is defined as the actual baseline visit.

The term ***'on-treatment period'*** refers to the period from the date of first administration of study treatment in the study to 7 days after the date of the last actual administration of any study treatment.

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

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

For display of summary statistics of endpoints by visit in overlaying individual plots and summary tables, a time window will be implemented to match the actual visit to its closest nominal visit. For Part A, +/- 7days of each nominal visit will be considered as the length of time window. For Part B the +/-7-day time window for the first 2 visits will be applied, while +/-14-day window will be applied to the next 2 visits and a +/-28-day window to the remaining ones. Out-of-window EOT data will be matched to the closest planned visit if it falls within the respective window. However, out-of-window F/U and EOS data will not be matched to other time points since patients will discontinue treatment starting with EOT.

2.2 Analysis sets

The following analysis sets will be defined for the statistical analysis conducted separately for each study part/cohort:

The Full Analysis Set (FAS) and Safety Set are defined in the same way and comprise all patients who received at least one dose of study treatment.

The PK analysis set will include all participants with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations or adverse events (for example, vomiting with 4 hours of dosing) which may impact iptacopan PK.

The PD analysis set will include all participants who received any study drug and with no protocol deviations with relevant impact on PD data.

If a participant received rescue medication during the treatment period, the values of [redacted] collected within 30 days following the end day of rescue medication will be treated as missing. If end day is not available, the values collected within 30 days following the start day of rescue medication will be treated as missing. This rule will be applied to PD Analysis.

The number and frequency (%) of participants in each analysis set will be presented. Participants with major protocol deviations will be presented for all participants.

2.2.1 Subgroup of interest

Besides the all group analysis, the following subgroups will be considered only for ITP participants (Cohort 1):

- sC5b-9 high stratification group
- sC5b-9 low stratification group

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number and percentage of participants in the safety analysis set who completed the study or prematurely discontinued, and the reason for discontinuation, will be presented.

2.3.2 Demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by cohort and group.

Disease characteristics will include:

For ITP cohort: Number of unique prior therapies, number of background therapies, and baseline platelet count and sC5b-9 levels at screening.

For CAD cohort: Number of unique prior therapies, number of background therapies, and baseline hemoglobin, LDH and total bilirubin values.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be listed by participant and summarized by system organ class and preferred term, by cohort and group.

2.3.2.1 Definition of unique prior therapy

A unique prior therapy is defined as any pharmaceutical agent or type of non-pharmacological intervention (e.g., splenectomy, plasmapheresis) administered with the intention to treat the indications under study (i.e. primary ITP for Cohort 1 or primary CAD for Cohort 2). Transfusions of blood products are not accounted as prior therapies. Any unique prior therapy will be counted once, even if it is stopped and restarted or given in different combinations. Different corticosteroids will be counted as a single unique prior therapy, whereas different members of other drug classes such as thrombopoietin receptor agonists will be counted as different unique prior therapies. The total number of unique prior therapies administered to each patient will be captured in the eCRF.

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

2.4.1 Study treatment / compliance

The duration of exposure in weeks to iptacopan will be summarized by means of descriptive statistics. Duration of exposure will be categorized by cohort and group as follows: <4 weeks, ≥4/<9 weeks, ≥9/<12 weeks.

2.4.2 Prior, concomitant and post therapies

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed by participant and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by cohort and group.

The need and use of rescue therapy will be assessed. The rescue therapy will be summarized by cohort, group and listed by cohort, group and visit/time point.

For cohorts allowing background therapy, this will be listed and summarized by cohort, participant, and visit/time. For Part B only, the ability to taper or discontinue any concomitant background therapy in responders will be listed and summarized.

The following decoded terms from field of medical history will be used to determine indication of ITP/CAD:

1. Immune thrombocytopenia
2. Cold type hemolytic anaemia

The definition for rescue therapy, prior therapy and background therapy are as follows:

- **Rescue therapy**: any therapy with above listed indications started on or after Day 1.
- **Unique prior therapy**: any therapy with above listed indications started before Screening visit.
- **Background therapy**: any therapy with above listed indications started before Day 1 and ongoing during treatment (from Day 1 and onwards). Also check for PD for the subject.

For Prior or Concomitant non-drug therapies/procedures, System or Organ Class is considered instead of ATC class since the latter is not collected for procedures. Also, for procedures, additional derivation logic was added to not consider transfusion data for prior and background therapy and to exclude SOC "Investigations" while flagging the therapies.

The unique prior therapies will be sorted by descending frequency.

2.5 Analysis supporting primary objective(s)

The primary objective of the study is to assess the efficacy of iptacopan in participants with benign hematological disorders such as primary ITP and primary CAD with an increase in platelet count and in hemoglobin being considered a favorable outcome in ITP and CAD participants, respectively.

2.5.1 Primary endpoint(s)

The primary efficacy endpoints of this study are:

- Cohort 1 (ITP): A clinically meaningful response, defined by a platelet count of ≥50 k/µL sustained for at least 2 consecutive weeks during the main, 12-week treatment part without the use of rescue therapy.
- Cohort 2 (CAD): A clinically meaningful response, defined by a hemoglobin level increase of ≥1.5 g/dL above baseline sustained for at least 2 consecutive weeks during the main, 12-week treatment part without the use of rescue therapy.

A study participant will be considered a responder if he/she meets all of the below criteria:

Cohort 1 (ITP):

1. Platelet count of ≥50 k/µL sustained for at least 2 consecutive weeks during the main, 12- week of treatment part;
2. Absence of rescue therapy or prohibited medications to treat ITP;
3. Lack of treatment discontinuation.

Cohort 2 (CAD):

1. Hemoglobin level increase of ≥1.5 g/dL above baseline sustained for at least 2 consecutive weeks during the main, 12-week treatment part;
2. Absence of rescue therapy or prohibited medications to treat CAD;
3. Lack of treatment discontinuation.

For both cohorts, occurrence of any of the events #2-3 prior to meeting event #1 would make the study participant a non-responder, whereas occurrence after would not affect his/her qualification as a responder with respect to the primary endpoint.

Descriptive analysis

For calculation of the success rate for the primary endpoint, all participants enrolled in the study in respective cohorts will be included.

The number and proportion of responders will be determined and summarized/listed by cohort.

Cohort 1 (ITP)

For the purpose of this study, a positive sign of efficacy in primary ITP participants is defined as an observed response rate of at least 30% in all-comers, or 50% in the participants with activated complement at screening.

The platelet counts will be summarized by visit and time point for both groups in Cohort 1 separately and combined. Summary statistics will be presented for raw and change from baseline for platelet counts by group, visit and time point and combined for both groups.

Cohort 2 (CAD)

For the purpose of this study, a positive sign of efficacy in primary CAD participants is defined as an observed response rate of at least 50%.

The hemoglobin levels will be summarized by visit and time point. Summary statistics will be presented for raw and change from baseline hemoglobin levels by visit and time point.

2.5.2 Statistical hypothesis, model, and method of analysis

Not applicable. The statistical evaluation of all primary efficacy data will be descriptive. Hypothesis testing will not be performed.

2.5.3 Handling of intercurrent events

The intercurrent events of the primary estimands are part of the primary variable, defined in Section 2.5.1.

2.5.4 Handling of missing values not related to intercurrent event

The analysis will include all available data up to the point of treatment discontinuation for participants who permanently discontinue. Descriptive statistics will not be adjusted for missing values.

2.6 Analysis supporting secondary objectives

The secondary PD objectives of the study are:

- To assess the time to first response
- To assess the duration of response during Part A
- To assess the magnitude of response during Part A
- Cohort 2 only: To assess the effect of iptacopan on relevant disease biomarkers (BM) not covered in the primary objective during Part A

2.6.1 Secondary endpoint(s)

2.6.1.1 Time to the first response

Cohort 1: The first time that a participant has a platelet count ≥50 k/µL will be collected.

Cohort 2: The first time that a participant has a hemoglobin level ≥1.5 g/dL above baseline will be collected.

Descriptive analysis

Time to the first response will be summarized from responders only. Summary statistics will be provided for the time to first response by cohort and group. In addition, time to response will be listed and presented graphically using a swimmer plot for all the participants by cohort and group.

2.6.1.2 Duration of response during Part A

Cohort 1: The duration of time during which a participant's platelet count remains ≥50 k/µL without the use of rescue therapy will be collected.

Cohort 2: The duration of time during which a participant's hemoglobin level remains ≥1.5 g/dL above baseline without the use of rescue therapy will be collected.

Descriptive analysis

Duration of response will be summarized for responders only. The duration of response would be considered as cumulative if there are non-continuous periods of response. For each visit up to Week 5, the duration of response will be considered 1 week (7 days) and, for each visit from Week 7 onwards, it will be considered 2 weeks (14 days). Summary statistics will be provided for duration of response by cohort and group. In addition, duration of response will be listed and presented graphically using a swimmer plot for all the participants by cohort and group.

2.6.1.3 Magnitude of response during Part A

Cohort 1: The magnitude of increase in platelet counts compared to baseline will be derived for each participant at each visit and time point.

Cohort 2: The magnitude of increase in hemoglobin levels compared to baseline will be derived for each participant at each visit and time point.

Descriptive analysis

The magnitude of increase from baseline of platelet counts and hemoglobin levels respectively will be summarized by cohorts and group. In addition, the magnitude of response will be categorized and summarized by cohort and group as below:

For ITP, absolute platelet counts <50, ≥50/<100, ≥100/<150, and ≥150 k/uL.

For CAD, Hb increase from baseline by <1, ≥1 and <1.5, ≥1.5 and <2, and ≥2 g/dL, as well as absolute Hb <10, ≥10/<12, ≥12 g/dL, and ≥LLN for each gender.

2.6.1.4 Effect of iptacopan on relevant disease biomarkers (BM) not covered in the primary objective during Part A

For Cohort 2-CAD only: Lactate dehydrogenase (LDH), total bilirubin, reticulocyte count and haptoglobin.

Descriptive analysis

Please refer to Section 2.9.3.

2.6.2 Statistical hypothesis, model, and method of analysis

Not applicable. The statistical evaluation of all secondary efficacy data will be descriptive. Hypothesis testing will not be performed.

2.6.3 Handling of intercurrent events

The intercurrent events of the primary estimands are part of the secondary variables, defined in Section 2.6.1.

2.6.4 Handling of missing values not related to intercurrent event

The analysis will include all available data up to the point of treatment discontinuation for participants who permanently discontinue. Descriptive statistics will not be adjusted for missing values.

2.7 Safety analyses

All participants within the Safety analysis set will be included in the safety data analysis. All listings and tables will be presented by cohort (for ITP, both groups (sC5b-9 high and sC5b-9 low) will be pooled).

The assessment of safety is based on the type and frequency of Adverse Events (AEs) as well as on the number of laboratory values that fall outside of pre-determined ranges (Common Toxicity Criteria for Adverse Events (CTCAE version 5.0) grading limits or normal ranges as appropriate). Other safety data include electrocardiogram and vital signs.

2.7.1 Adverse events (AEs)

2.7.1.1 Data handling

Adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) and assessed according to severity grade: mild/moderate/severe, respectively.

Note: The latest available MedDRA version at the time of the analyses will be used. The MedDRA version used will be specified in the footnote of relevant tables.

2.7.1.2 Data analysis

All information obtained on adverse events will be displayed by cohort, group and participant.

The number (and percentage) of participants with treatment-emergent adverse events (events started after the first dose of study medication but increased in severity based on preferred term) will be summarized in the following ways.

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

SOC will be sorted by descending frequency. PTs within SOC will be sorted by descending frequency in Investigational drug column of highest relevance, and within that column by subgroup of highest relevance (e.g. subgroup with highest N).

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation, and adverse events leading to dose adjustment.

A participant with multiple adverse events within a primary SOC is only counted once towards the total of the primary SOC and cohort.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment -emergent adverse events which are not serious adverse events with an incidence greater than 5% and on treatment-emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

Adverse events which will be counted for a specific treatment period are those which are treatment-emergent. These events are those with an onset after the start of the treatment period, or which were present prior to the start of the treatment period but increased in severity, changed from being not suspected to being suspected of study drug relationship, or developed into SAEs after the start of the treatment period. For the AE/SAE reporting, post-treatment will be considered to be any events that started or increased in severity after the end of the on-treatment period (i.e. more than 7 days after the last dose of study medication).

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

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

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

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

2.7.1.2.1 Adverse events of special interest / grouping of AEs

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are of scientific and medical interest specific to Novartis's product or program, for which ongoing monitoring may be appropriate. Such events may require further investigation in order to characterize and understand them. AESI for iptacopan are defined on the basis of potential safety risks for the product, class effects, and data from preclinical studies.

The number (and proportion) of participants with AESI, including serious adverse events of special interest will be summarized by cohort. The frequency and percentage of participants

with treatment emergent adverse events of special interest (TEAESI) and serious TEAESI will be summarized by PT.

A listing of participants experiencing AESIs will also be provided by cohort. The eCRS safety topic definitions used to identify AESIs will be provided as a listing. The Compound Case Retrieval Strategy (CRS) will be used to determine the MedDRA search criteria to be used to identify events of special interest (using the "SP" flag). The most recent list of AESI at the time of database lock will be used.

2.7.2 Deaths

A summary for deaths, including on-treatment and post-treatment deaths will be provided in case deaths occur during the study.

2.7.3 Laboratory data

2.7.3.1 Data handling

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The calculation of laboratory CTC grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTC grades are given in "Novartis internal criteria for CTC grading of laboratory parameters". The latest available version of the document based on the underlying CTCAE version 5.0 at the time of analysis will be used.

For laboratory tests where grades are not defined by CTCAE v5.0, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 is not applicable (deaths will be summarized separately). For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

2.7.3.2 Data analysis

All laboratory data will be listed by cohort, group, participant, and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing is provided presenting all parameters in a participant with any abnormal values. Summary statistics will be provided for all laboratory data by cohort, group and visit/time. For all continuous laboratory parameters, the absolute on-treatment laboratory values will be summarized with standard descriptive statistics (mean, median, standard deviation, minimum, maximum) by parameter, and scheduled visit/time point.

Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value. Shift tables using CTCAE grading (version 5.0) 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 (e.g. LDL, HDL) will also be provided to show patients with a change from normal to abnormal

Boxplots to visualize trends in laboratory data will be created.

On analyzing laboratory data from all sources (central and local laboratories (as applicable)) will be combined. 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. The summaries will include all assessments available for the lab parameter collected no later than last day of the on-treatment period.

The following summaries will be produced for hematology and biochemistry laboratory data (by laboratory parameter and treatment):

- Worst post-baseline CTC grade (regardless of the baseline status). Each subject will be counted only for the worst grade observed post-baseline.
- Shift tables using CTC grades to compare baseline to the worst on-treatment value
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

HIV tests and hepatitis markers are only collected at screening and no shift tables nor box plots will be produced. For Urinalysis tests, shift table and box plot will not be produced either.

Laboratory parameters with a CTCAE grade are listed in Table 2-1. Laboratory parameters with no CTCAE grade are listed in Table 2-2.

Table 2-1 Laboratory parameters with a CTCAE grade

Test Category	Laboratory Parameters
Hematology	Hemoglobin, Platelets, Leukocytes, Differential (Lymphocytes, Neutrophils), Prothrombin International normalized ratio (INR), Activated partial thromboplastin time (APTT)
Chemistry	Albumin, Alkaline phosphatase (ALP), ALT, AST, Gamma-glutamyl-transferase (GGT), Calcium, Magnesium, Sodium, Potassium, Creatinine, Creatine kinase, Total Bilirubin, Total Cholesterol, Triglycerides, Amylase, Glucose, Haptogloblin (Cohort 2 CAD only), estimated GFR
Urinalysis	Protein

Table 2-2 Laboratory parameters with no CTCAE grade

Test Category	Laboratory Parameters
Hematology	Ery. Mean Corpuscular Volume, Erythrocytes, Erythrocyte Cell Morphology (if available at local lab and indicated based on flagged blood count results), Differential (Basophils, Eosinophils, Monocytes, Bands), Reticulocytes (selected visits as per assessment schedule) Ery. Mean Corpuscular HGB Concentration, Ery. Mean Corpuscular Hemoglobin, Hematocrit, Prothrombin Time
Chemistry	Direct Bilirubin, Indirect Bilirubin, Lactate dehydrogenase (LDH), Urea Nitrogen or Urea, Uric Acid, Phosphate, Chloride, Ferritin, Lipase, Dihydrotestosterone (DHT), Follicle Stimulating Hormone, Hepatitis B Virus Surface Antigen (HBsAg), Hepatitis C Virus (HCV) antibodies, Luteinizing Hormone (LH), Testosterone, thyroxine (T4), Triiodothyronine (T3), TSH, reverse T3

The newly occurring liver enzyme abnormalities will be summarized by cohort. The categories of abnormalities are described in Table 2-3. For a participant to meet the criterion of a newly occurring clinically notable value, the participant needs to have a baseline value which is not clinically notable for that parameter. For a participant to meet the criterion of a worsening clinically notable value, the participant needs to have a baseline value which is clinically notable as well as a worsened post-baseline value. For participants with a missing baseline value, any post-baseline notable value will be considered as newly occurring.

Table 2-3 Definition of liver toxicities based on laboratory parameters

Definition
ALT >3x ULN
ALT >5x ULN
ALT >10x ULN
ALT >20x ULN
AST >3x ULN
AST >5x ULN
AST >10x ULN
AST >20x ULN
ALT or AST >3x ULN
ALT or AST >5x ULN
ALT or AST >8x ULN
ALT or AST >10x ULN
ALT or AST >20x ULN
Total bilirubin (BILI) >2x ULN
Total bilirubin (BILI) >3x ULN

ALP >2XULN (>3XULN in the presence of bone pathology*)
Combined elevations post-baseline
AST and ALT =< ULN at baseline
ALT or AST >3x ULN & BILI >2x ULN
ALT or AST >3x ULN & BILI >2x ULN & ALP <2x ULN
ALT or AST >3x ULN & BILI >2x ULN & ALP >=2x ULN
ALT or AST > ULN at baseline
ALT or AST >3x Bsl or 8x ULN & BILI (>2x Bsl and 2x ULN)
ALT or AST >3x Bsl or 8x ULN & BILI (>2x Bsl and 2x ULN) & ALP <2x ULN
ALT or AST >3x Bsl or 8x ULN & BILI (>2x Bsl and 2x ULN) & ALP >=2x ULN
* the presence of bone pathology is confirmed by reported AEs or medical history of HLGT = "Bone disorders (excl congenital and fractures)" with a start date prior to laboratory measurement and stop date posterior to laboratory measurement

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 is only 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 <2x ULN 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).

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each participant during the study. ECG data will be read and interpreted locally.

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

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

- HR decrease from baseline ≥ 25%
- HR > 130 bpm

In addition, a listing of these participants will be produced by cohort and group.

All ECG data will be listed by cohort, group, participant, and visit/time; abnormalities will be flagged. Summary statistics will be provided by cohort, group and visit. In addition, the number and percentage of patients with notable ECG changes from baseline and a listing of ECG intervals will be presented by cohort.

2.7.4.2 Vital signs

Vital signs measurements include systolic blood pressure (SBP) and diastolic blood pressure (DBP), pulse rate, body temperature, height, and body weight. All vital signs data will be listed by cohort, group, participant, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics (absolute on-treatment values and change from baseline) for the on-treatment period will be provided by cohort, group and 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. The change from baseline to worst post-baseline value and shift tables based on notable values will be summarized.

Boxplots to visualize trends in vital signs data will be created.

2.8 Pharmacokinetic endpoints

All participants in the PK analysis set (PAS) will be included in the PK data analysis. The PAS will be defined separately for each cohort.

The following plasma pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 8 or higher):

- AUClast, AUCtau, Cmax, Ctrough, Tmax.

Other pharmacokinetic parameters may be calculated as appropriate. The linear trapezoidal rule will be used for AUC calculations.

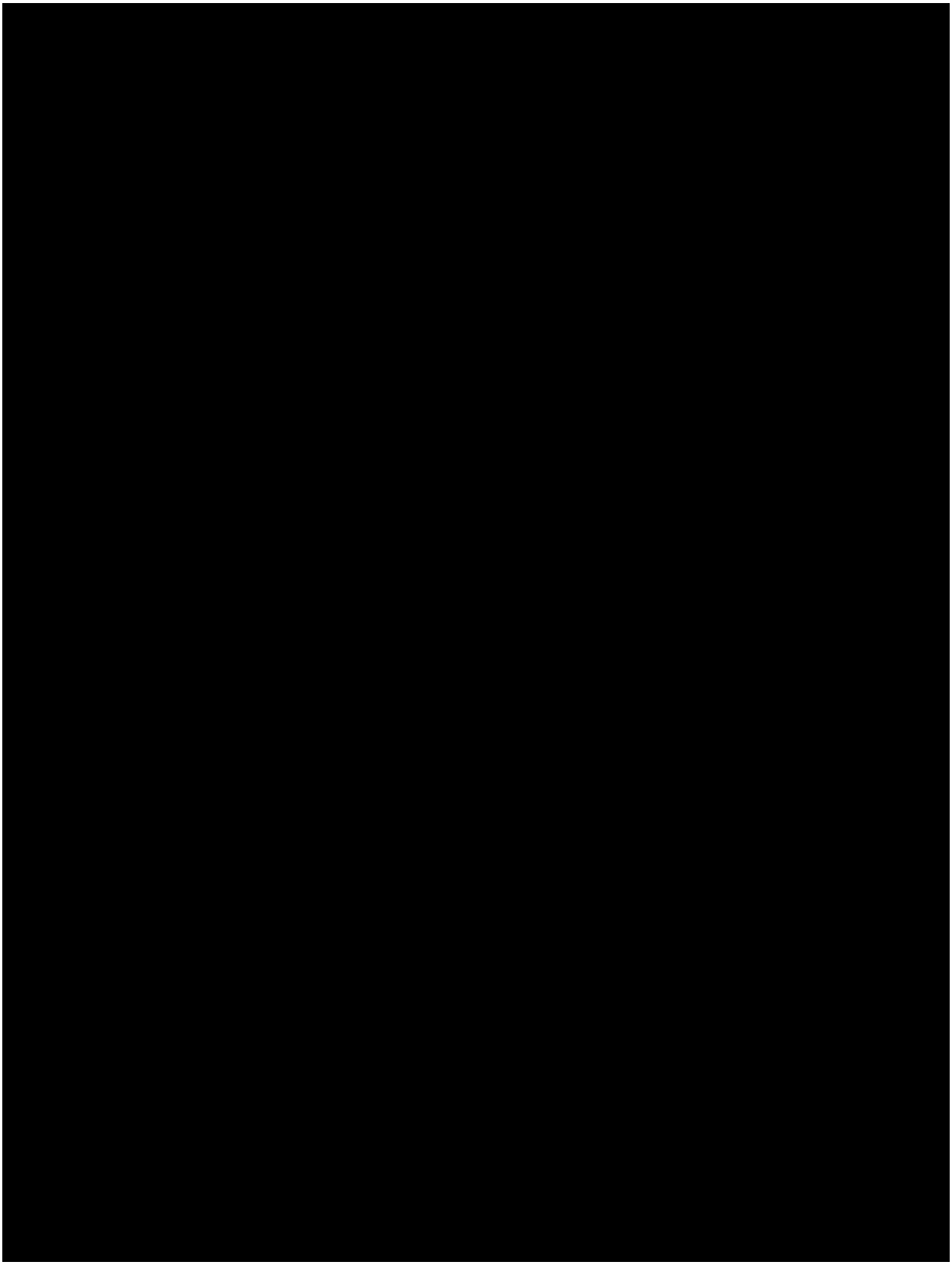
AUCtau will be calculated by the "last observation carried forward" approach, assuming that, at steady-state, the iptacopan plasma concentration at T=12hr (tau) is the same as the profile's corresponding pre-dose (T=0) value. The approach will be applied because sampling times are limited to 6 hours postdose and the extrapolation of AUClast (0-6hrs) to AUCtau (0-12hrs) is likely to exceed the accepted value of 20% of the total AUC and be based on an unreliable half-life estimate.

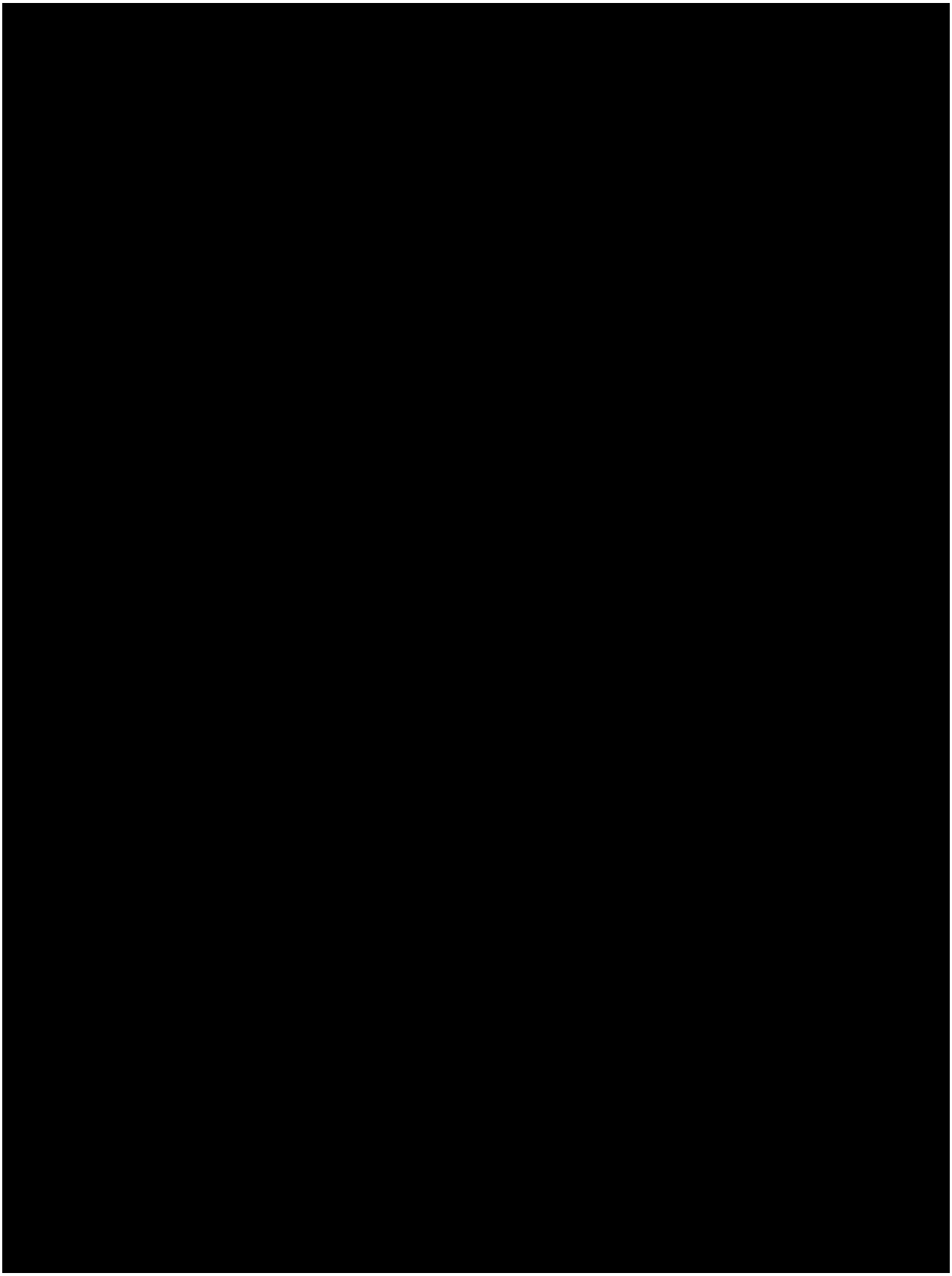
Descriptive analyses

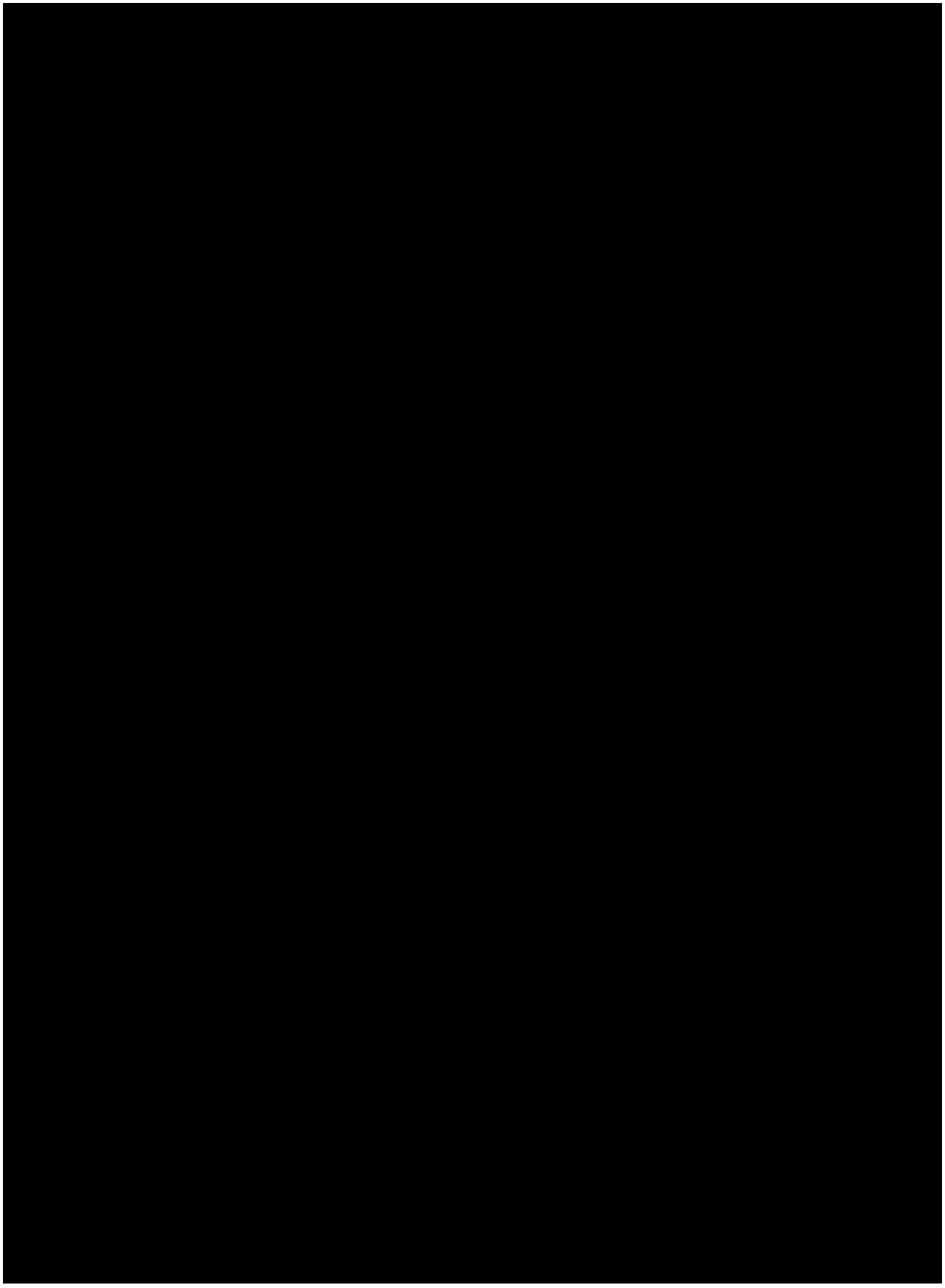
Individual iptacopan plasma concentrations and PK parameters will be listed by cohort, participant, and visit/sampling time point.

Descriptive summary statistics of iptacopan plasma concentration data (unbound concentrations as available) will be provided by cohort and visit/sampling time point, including the number of subjects with evaluable values (n) and the number of subjects with quantifiable concentrations (≥LLOQ) (m). Summary statistics for concentration-time data will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations. Zero concentrations will be considered as missing for the geometric mean and geometric CV% calculations. Graphical methods will be employed to show mean and individual concentration-time profiles.

Descriptive summary statistics for PK parameters will include mean (arithmetic and geometric), between-subject SD, and between-subject CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is Tmax where only median, minimum, and maximum will be presented. Additionally, within-subject SD and CV (arithmetic and geometric) will be presented for Ctrough.







2.10 Interim analysis

The following IAs are planned for each cohort:

- An interim analysis is planned after approximately half of the participants within a cohort complete 12 weeks of treatment. For these participants the efficacy data up to week 12 (along with relevant safety and potentially PK data) will be examined as a preliminary evaluation of proof of concept (PoC).
- A second interim analysis is planned after all participants within a cohort complete 12 weeks of treatment. Relevant data up to Part A EOS will be examined.

Additional IAs may be conducted to support decision making concerning the current clinical study, the sponsor's clinical development projects in general, or in case of any safety concerns.

The clinical team may communicate interim results (e.g., evaluation of PoC criteria or information needed for planning/modifying another study) to relevant Novartis teams for information, consulting and/or decision purposes.

Interim results may be used to prepare publications, abstracts and/or presentations at scientific meetings.

3 Sample size calculation

3.1 Primary endpoint(s)

3.1.1 Cohort 1: ITP (N=20)

Approximately 20 participants diagnosed with primary ITP and sustained thrombocytopenia will be enrolled. Participants will be stratified based on complement activation (sC5b-9 levels) at screening in to one of the two groups (complement-activated vs. not complement-activated) until approximately 10 participants have been assigned to each group.

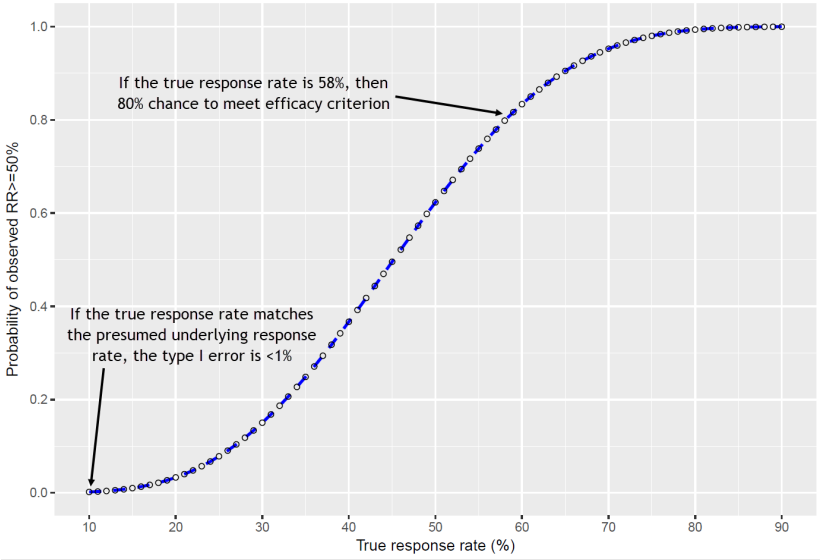
Complement-activated group (N=10):

With 10 participants, this group has 80% probability to meet the efficacy criterion of 50% or more responders if the true response rate is 58%. For lower true response rates, the probability of having at least 50% responders is appropriately lower; for example, 62%, 37% and 15% for true response rates of 50, 40 and 30%, respectively.

With 10 participants,

- the probability of a false-positive readout (i.e., probability of meeting the efficacy criterion, when the true response rate with iptacopan treatment is smaller or equal to the presumed underlying response rate of 10%) is < 1%.
- the probability of a false-negative readout (i.e., probability of not meeting the efficacy criterion, when the true response rate is at least 58%) is 20%.

Figure 3-1 Probability of observed response rate of ≥50 percent vs. true response rate



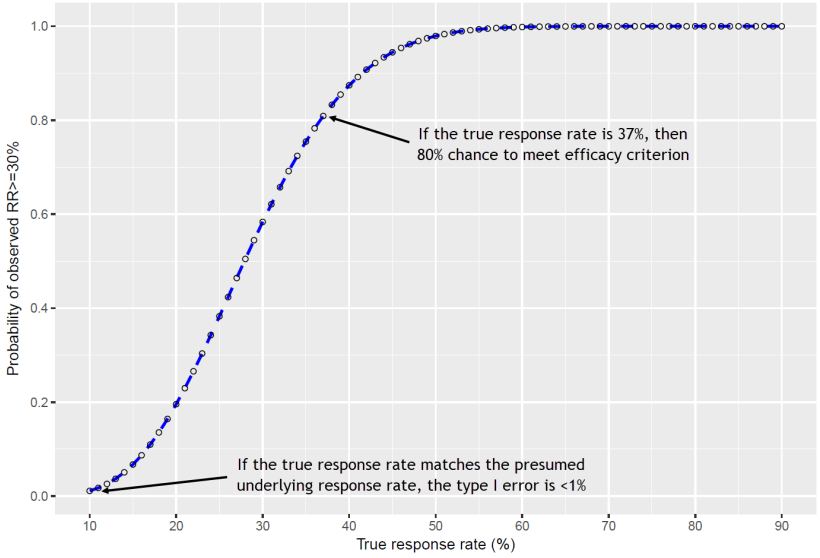
All-comers (N=20):

With 20 participants, the combined groups (full cohort) have 80% probability to meet the efficacy criterion of 30% or more responders if the true response rate is 37%. For lower true response rates, the probability of having at least 30% responders is appropriately lower; for example, 58.4% and 20% for true response rates of 30 and 20% respectively.

With 20 participants,

- the probability of a false-positive readout (i.e., probability of meeting the efficacy criterion, when the true response rate with iptacopan treatment is smaller or equal to the presumed underlying response rate of 10%) is 1%.
- the probability of a false-negative readout (i.e., probability of not meeting the efficacy criterion, when the true response rate is at least 37%) is 20%.

Figure 3-2 Probability of observed response rate of ≥30 percent vs. true response rate



4 Change to protocol specified analyses

No changes from protocol specified analysis were made.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

No imputations will be done for the treatment start and end dates.

5.1.2 AE date imputation

As per Novartis standard AE date imputation rules, the following matrix explains the logic behind the imputation.

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

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

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

Rules for imputing the 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.

Rules for imputing the AE end date:

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, 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 (treatment follow up period date, 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.

5.1.3 Concomitant medication date imputation

As per Novartis standard Concomitant medication 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	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY=TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.a) Uncertain	(4.c) After Treatment Start
YYYY>TRTY	(3.a)	(3.b)	(3.b)	(3.b)

	After Treatment Start	After Treatment Start	After Treatment Start	After Treatment Start

Rules for imputing the CM start date:

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.

Rules for imputing the CM end date:

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

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

The above imputation rules apply to both prior therapies and post therapies.

[redacted]

5.2 AEs coding/grading

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The AEs will be graded as Mild, Moderate and Severe for the severity grade.

5.3 Laboratory parameters derivations

The laboratory parameters derivations will be performed by the Central Lab.

In order to minimize the risk of spontaneous RBC agglutination in vitro, hematology samples from CAD patients will be analyzed at local clinical diagnostic laboratories for the following parameters: complete blood count, reticulocytes and DAT. All CAD samples will be processed per specific instructions as outlined in the lab manual.

If participants cannot visit the site for protocol-specified safety lab assessments, an alternative (local) laboratory may be used for safety sample collection. Where samples are collected and

analyzed at a local instead of the central laboratory, Novartis will ensure the results reported are equivalent to central laboratory collection and analysis.

Any quantitative clinical laboratory values given as "<X.X> or <X.X or >X.X" in the database will be imputed with the value of the number without the sign for the descriptive statistics and the calculation of changes from baseline, e.g., a value of "<2.2" will be imputed as 2.2 for the calculations.

There will be no imputation in the data listings; all values will be displayed as recorded in the database. This is not applicable for lab parameter that falls under qualitative category.

5.4 Statistical models

5.4.1 Analysis supporting primary objective(s)

Not applicable.

5.4.2 Analysis supporting secondary objective(s)

Not applicable.

5.5 Rule of exclusion criteria of analysis sets

All PDs will be assessed before database lock to determine whether these deviations may warrant the exclusion of a participant from the statistical analyses or summary statistics:

Table 5-1 Criteria leading to exclusion

Analysis Set	Criteria that cause participants to be excluded
PK	INCL01: Deviation from inclusion criterion 1 (Written informed consent must be obtained before any assessment is performed)
PD	INCL01: Deviation from inclusion criterion 1 (Written informed consent must be obtained before any assessment is performed) EXCL102: No ITP-directed background therapy permitted, with the exception of either a single thrombopoietin receptor agonist (TPO-RA) or low-dose corticosteroid (prednisone-equivalent of ≤10 mg daily), as long as stable dosage for at least 4 weeks prior to first iptacopan dose.
Safety	INCL01: Deviation from inclusion criterion 1 (Written informed consent must be obtained before any assessment is performed)

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

6 Reference

1. Clinical Study Protocol, CLNP023L12201, Protocol Version v03, 26 Apr 2022.