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LNP023

Clinical Trial Protocol 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

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List of abbreviations

ADCC	Antibody-Dependent Cellular Cytotoxicity
AE	Adverse Event
AESI	Adverse Events of Special Interest
aHUS	Atypical Hemolytic Uremic Syndrome
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AP	Alternative (complement) Pathway
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
b.i.d.	Bis in die/twice a day
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BDR	Bioanalytical Data Report
BM	Biomarker
BMI	Body Mass Index
C1	Complement Component 1
C3	Complement Component 3
C3G	C3 Glomerulopathy
C4	Complement Component 4
C5	Complement Component 5
CAD	Cold Agglutinin Disease
CK	Creatinine Kinase
CKD	Chronic Kidney Diseases
[redacted]	[redacted]
CMO&PS	Chief Medical Office and Patient Safety
CO	Country Organization
[redacted]	[redacted]
CP	Classical (complement) Pathway
CRO	Contract Research Organization
CSR	Clinical Study Report
CV	Coefficient of Variation
[redacted]	[redacted]
DDC	Direct Data Capture
DHT	Dihydrotestosterone
DQF	Data Query Form
ECG	Electrocardiogram
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
eSAE	Electronic Serious Adverse Event
eSource	Electronic Source

[redacted]	
FB	Complement Factor B
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GGT	Gamma-Glutamyl Transferase
h	Hour
HBcAg	Hepatitis B core antigen
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgAN	IgA Nephropathy
iMN	Idiopathic Membranous Nephropathy
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
ITP	Immune Thrombocytopenia
[redacted]	
IVIG	Intravenous Immunoglobulins
k	Thousand, 10^3
k/µL	Thousand per Microliter, 10^3/µL
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LH	Luteinizing Hormone
LLOQ	Lower Limit of Quantification
LP	Lectin Pathway
MAC	Membrane Attack Complex
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
mL	milliliter(s)
NTI	Narrow Therapeutic Index
OHP	Off-site healthcare Professional
P-gp	P-glycoprotein

PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PNH	Paroxysmal Nocturnal Hemoglobinuria
PoC	Proof of Concept
[redacted]	[redacted]
PT	Prothrombin Time
QMS	Quality Management System
[redacted]	[redacted]
QTcF	QT interval corrected by Fridericia's formula
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sC5b-9	soluble Complement Component 5 fraction "b" linked to Complement Component 9
sCR	serum Creatinine
SD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
T3	Triiodothyronine
T4	Thyroxine
TBC	To be confirmed
TBL	Total Bilirubin
TPO-RA	Thrombopoietin Receptor Agonist
TSH	Thyroid Stimulating Hormone
TTP	Thrombotic Thrombocytopenic Purpura
ULN	Upper Limit of Normal
ULOQ	Upper Limit of Quantification
wAIHA	Warm Autoimmune Hemolytic Anemia
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
[redacted]	[redacted]
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed up or traced over time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
Electronic Source Direct Data Capture (eSource DDC)	Any technology that allows the capture of clinical study source data electronically by investigator site staff at the point of care, into an electronic form that has been validated to capture clinical data.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant.
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well

	as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Hybrid Trial Design	Flexible model incorporating both onsite (traditional site based) and off-site (decentralized) elements within the same study design
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Off-site	Describes trial activities that are performed at an off-site location by an off-site healthcare professional, such as procedures performed at the participant's home.
Off-site healthcare Professional (OHP)	A qualified healthcare professional, such as include those used in the study e.g. Nurse, Phlebotomist, Physician, who performs certain protocol procedures for the participant in an off-site location such as a participant's home.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
[redacted]	[redacted]
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource

Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Telemedicine	Electronic information and telecommunications technologies (both video-based and audio-only) to facilitate the delivery of health care and health related education where participant and health care professional are not in the same location.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Unique Prior Therapy	Any pharmaceutical agent or type of non-pharmacological intervention (e.g., splenectomy, plasmapheresis) administered with the intention to treat the indications under study. 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.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

Amendment 3 (April 2022)

Amendment rationale

The purpose of this amendment is to update the eligibility criteria related to liver disease or injury as follows:

- As per the inclusion criteria, Cohort 2 CAD participants are required to have ongoing hemolysis with elevated LDH or total bilirubin at baseline. Though high serum aspartate transaminase (AST) is typically considered a biomarker of hepatocellular damage, it may also be elevated due to hemolysis only. To account for this, the acceptable levels for AST have been increased from 2x to 5x upper limit of normal (ULN) for CAD participants.
- In addition, for all participants, the acceptable limit for the liver enzymes (ALT, AST, GGT, alkaline phosphatase) was increased from 2x to 2.5x ULN to account for the patient populations of interest, particularly for participants with cold agglutinin disease, who may be expected to have mildly elevated liver enzymes.

This amendment also incorporates the following changes:

- In non-malignant hematological diseases, the prior administered therapies are more commonly referred to as unique prior therapies rather than lines of prior therapies. These are defined as any pharmaceutical agent or type of non-pharmacological intervention administered with the intention to treat the indications under study. To align with this more commonly used terminology, the respective inclusion criterion has been updated accordingly for both ITP and CAD participants.
- As the screening period can last up to 8 weeks and during this period study participants may require the administration of rescue therapy, additional wording has been added to the relevant sections in the protocol in order to further clarify the time when rescue therapy may be administered in relation to treatment initiation.

Other minor changes have been incorporated to improve clarity and correct inconsistencies.

Study Status

The study has started enrollment on 21-Dec-2021. As of March 2022, 1 ITP and 3 CAD participants have been treated in the study.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- The Glossary of terms was updated to include the definition of unique prior therapy and to remove the premature participant withdrawal since it is not used in the protocol.
- The protocol summary was updated to reflect the modifications of the main document.
- Section 1.1.2: Correction was made to list red blood cell transfusions as a supportive therapy for cold agglutinin disease.

- Section 5.1.1: Inclusion criteria 102 and 205 have been updated to further define the prior therapies for ITP and CAD participants. Section 2.1 has been updated to reflect this change.
- Section 5.2: Exclusion criterion 18 has been updated to allow AST values up to 5xULN for CAD participants if attributed to ongoing hemolysis alone. The allowed values for the liver function parameters have been updated to up to 2.5xULN for all participants.
- Section 5.2.1: The wording in the exclusion criterion 102 has been updated to provide better clarity for the permitted ITP-directed background therapy and to align with the changes in Table 6-2. Section 3.1.1 and Section 4.1.1 have been updated accordingly to reflect this change.
- Section 6.2.2 – Table 6-2. For better clarity, the definition of the period for the prohibited medications has been updated from baseline to first iptacopan dose.
- Section 6.2.3: Clarification has been added for the use of rescue therapy during the screening period.
- Table 8-1: The assessments of blood pressure and pulse rate have been added to the baseline visit as per exclusion criterion 22.
- Section 10.1.3: The option of the paper backup Serious Adverse Event (SAE) Report form is added for the SAE reporting.
- Section 12.4.2: Correction was made that for the calculation of the success rate for the primary endpoint, all participants who were treated in the study will be included.
- Section 12.5.1.1: Correction was made that time to first response will be presented.
- Section 16.2 – Table 16-1: Action required for Jaundice related to hospitalization has been updated to align with the rest of the table.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 2 (December 2021)

Amendment rationale

The purpose of this amendment is to address a comment received from South Korean Health Authority (HA):

- Inclusion criterion #102 was supplemented with South Korea specific instructions. Participants must have received at least 2 prior lines of ITP-directed therapy, unless they do not qualify for available second-line treatment options per the investigator's assessment.

In addition, other changes have been incorporated to improve clarity and correct inconsistencies.

Changes to the protocol

- The protocol summary was updated to reflect the modifications of the main document.
- Section 2: It was clarified that PK will be assessed in the respective target populations as available data suggest that exposure may differ between indications.
- Section 3.2 and Section 4.1.2: Off-site procedures are not applicable to Cohort 2 because CAD blood samples require incubation at 37-39°C immediately upon collection until further processing and/or analysis to minimize the risk of spontaneous *in vitro* RBC agglutination. This cannot be supported at off-site locations, nor during transportation to the analyzing lab. Same change applied in Section 7, Table 8-1 and Table 8-3.
- Section 5.1.1: Inclusion criterion #102 was supplemented with South Korea specific instructions as per request from South Korean HA participants must have received at least 2 prior lines of ITP-directed therapy, unless they do not qualify for available second-line treatment options per the investigator's assessment.
- Section 5.1.2: Inclusion criterion #201 was amended to include more detailed definitions of splenomegaly, hepatomegaly and lymphadenopathy as recommended by investigators.
- Section 6.2.1.1: Section was updated to correct that CYP2C8 is most prominent route of iptacopan metabolism. This aligns this section with Table 6-2.
- Assessment schedules:
  - Table 8-1: Footnote #3 has been split in two footnotes (#3 and #7) to increase clarity.
  - Table 8-1 and Table 8-3: Timing of follow-up call was updated to align with Section 3 and Section 10.1.3. Follow-up call is conducted 30 days after last visit.
  - Table 8-2 and Table 8-3: Timing for some PK samples was clarified to be directly before dosing (0 hours).
  - Table 8-3: Remote visit is out of scope on Day 29 in Part B due to physical examination for Cohort 1.
- Section 8.1: Table 8-4 was added to simplify review of eligibility for HCV and HBV. In addition, clarification added that, for Cohort 2, local results can be used for eligibility.

- Section 10.1.3: SAE reporting wording was updated to consider different local requirements.
- Section 12.7: Interim analysis 2 details were updated to align with Section 4.4.
- Minor additions and corrections have been done throughout the protocol to increase clarity.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 1 (October 2021)

Amendment rationale

The purpose of this amendment is to address questions raised by the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM). The following changes were made to the inclusion/exclusion criteria:

- Inclusion criterion #101 was revised to clarify immune thrombocytopenia (ITP) should be persistent or chronic and diagnosed at least 3 months prior to baseline.
- Exclusion criterion #10 was revised to exclude participants with any severe concurrent co-morbidities.
- Several inclusion/exclusion criteria have been newly added:
  - To include participants with a weight of at least 35 kg
  - To exclude participants with active severe bleeding or history of intracranial hemorrhage.
  - To exclude participants with liver disease or liver injury as indicated by abnormal liver function tests
  - To exclude participants with unstable medical conditions such as myocardial ischemia or unstable thrombotic events to complement revised exclusion criterion #10
  - To exclude participants with an estimated Glomerular Filtration Rate (eGFR) of less than 45 mL/min/1.73 m^2
  - To exclude participants with ECG and vital signs out of range (as defined in exclusion criteria #21 and #22).

In addition to BfArM requests, the protocol is amended as per investigators comments to account for the high risk of spontaneous red blood cell agglutination in blood samples from cold agglutinin disease (CAD) patients at room temperature. The amendment will implement analysis of hematology samples (including complete blood count, reticulocytes, DAT) from CAD patients at local clinical diagnostic laboratories. This change will allow sites to maintain local routines whereby CAD patient samples are incubated at 37-39°C immediately upon collection until they are further processed and/or analyzed, thus minimizing the risk of spontaneous red blood cell agglutination *in vitro*.

Changes to the protocol

- The protocol summary was updated to reflect the modifications of the main document.
- Section 5.1: Addition of criterion #5 as described above.
- Section 5.1.1: Modifications of criterion #101 as described above.
- Section 5.2: Criteria #10 was updated and criteria #17-22 have been added as described above.
- Assessment schedules:
  - Table 8-1 and Table 8-3: Footnote and assessment schedule were updated to clarify local vs central analysis of hematology and DAT samples.

- Section 8.4.1: Section updated to allow for local lab to be used for Cohort 2 (see rationale above). Addition of estimated GFR to allow to determine eligibility based on new exclusion criterion.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Protocol summary

Protocol number	CLNP023L12201
Full Title	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
Brief title	A basket study to assess efficacy, safety and PK of iptacopan (LNP023) in autoimmune benign hematological disorders
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose	The main purpose of this study is to evaluate the efficacy and safety of iptacopan in participants with autoimmune benign hematological disorders such as primary immune thrombocytopenia (ITP) and primary cold agglutinin disease (CAD).
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 **Cohort 2:** To assess the ability of iptacopan to induce a clinically meaningful increase in hemoglobin levels in participants with primary CAD
Secondary Objectives	• 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 • To assess the need for rescue therapy during Part A • Cohort 2: To assess the effect of iptacopan on relevant disease biomarkers (BM) not covered in the primary objective during Part A • To assess the safety and tolerability of iptacopan in participants with benign hematological disorders • To assess the pharmacokinetics of iptacopan in the respective target populations
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 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).
Rationale	The rationale and purpose is to evaluate the efficacy and safety of iptacopan in participants with autoimmune benign hematological disorders such as primary ITP and primary CAD.

Study population	The study population will comprise a total of approximately 30 enrolled participants: • Cohort 1: Approximately 20 participants with primary ITP will be enrolled; approximately 10 participants each, with high and low complement activation, respectively. • Cohort 2: Approximately 10 participants with primary CAD will be enrolled.
Key Inclusion criteria	All Cohorts: • Written informed consent • Vaccination against *Neisseria meningitidis* and *Streptococcus pneumoniae* infections is required and vaccination against *Haemophilus influenzae* infection is recommended prior to the start of treatment. • Weight of at least 35 kg Cohort 1 specific inclusion criteria: • Male and female participants aged ≥ 18 years at baseline with a diagnosis of persistent or chronic primary ITP (diagnosed at least 3 months prior to baseline) • Participants must have received at least 1 unique prior therapy administered with the intention to treat ITP • Sustained thrombocytopenia Cohort 2 specific inclusion criteria: • Male and female participants aged ≥18 years at baseline with a diagnosis of primary CAD, including CAD arising in the setting of a low-grade lymphoproliferative disorder a) not requiring any therapy and b) without evidence of significant splenomegaly, hepatomegaly, or diffuse lymphadenopathy (as per Section 5.1.2) • Positive direct antiglobulin test for C3d only and cold agglutinin titer of ≥64 at 4°C • Laboratory evidence of ongoing hemolysis • Sustained anemia • Participants must have received at least 1 unique prior therapy administered with the intention to treat CAD
Key Exclusion criteria	All cohorts: • Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 30 days, whichever is longer; or longer if required by local regulations • Past or concomitant use of medications prohibited by the protocol • Known or suspected hereditary or acquired complement deficiency • History of primary or secondary immunodeficiency, including a positive HIV test result • Chronic infection with Hepatitis B or C virus • History of recurrent invasive infections caused by encapsulated organisms, including *N. meningitidis*, *S. pneumoniae*, or *H. influenzae* • Presence or suspicion (based on judgment of the investigator) of any active infection within 14 days prior to first study drug administration.

	• Any medical condition deemed likely to interfere with the participant's participation in the study • Any malignant disease diagnosed within the past 5 years, with the exception of localized non-melanoma skin cancer, *in situ* cervical cancer, or, for CAD, a low-grade lymphoproliferative disorder. • History of bone marrow/hematopoietic stem cell or solid organ transplantation. • Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of investigational drug and for 1 week after last iptacopan dose • Active severe bleeding or history of intracranial hemorrhage • Liver disease, or liver injury as indicated by abnormal liver function tests • Severe concurrent co-morbidities or unstable medical conditions Cohort 1 specific exclusion criteria: • Secondary ITP, as may arise in the setting of certain autoimmune disorders, immunodeficiency syndromes, infections, malignancies, and drug treatments • No ITP-directed background therapy permitted, with the exception of either a thrombopoietin receptor agonist (TPO-RA) or low-dose corticosteroid, as long as stable dosage for at least 4 weeks prior to first iptacopan dose • Abnormal coagulation screening labs (PT/INR, PTT). Cohort 2 specific exclusion criteria: • Secondary cold agglutinin syndrome, as may arise in the setting of certain infections, autoimmune disorders, and malignancies (with the exception of a low-grade lymphoproliferative disorder) • No CAD-directed background therapy permitted
Study treatment	Iptacopan 200 mg b.i.d.
Treatment of interest	The treatment of interest is iptacopan with or without the allowed background medication for the indication studied. The dose of the allowed background medication must remain stable during Part A and can be tapered after two weeks of treatment in Part B
Efficacy assessments	Cohort 1: Platelet count Cohort 2: Hemoglobin level
Pharmacokinetic assessments	The pharmacokinetic profile of iptacopan will be established in the different indications at two different visits in Part A, and PK parameters (AUCtau, AUClast, Cmax, Tmax) will be calculated from plasma samples collected up to 6 hours post dose.
Key safety assessments	Adverse event monitoring, physical examinations, vital signs, ECGs, monitoring of laboratory markers in blood and urine
Other assessments	[redacted]

	[redacted]
Data analysis	The primary 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. Use of any rescue therapy (see Section 6.2.3) before response criteria are met is considered an unfavorable outcome, and, therefore, the participants will be considered as non-responders. Conversely, use of rescue therapy after the primary endpoint is met, does not impact the response status with respect to that endpoint. A positive sign of efficacy will be defined separately for each cohort. In Cohort 1, this will be defined as having a response rate of at least 30% in all-comers, or 50% in the patients with activated complement at screening. In Cohort 2, this will be defined as a response rate of at least 50%. Additional analyses include the platelet count (Cohort 1) and hemoglobin levels (Cohort 2) which will be summarized by Cohort, group (if applicable), visit and time point. This will be done for both the raw values and change from baseline.
Key words	Iptacopan, LNP023, Benign Hematology, Immune Thrombocytopenia (ITP), Cold Agglutinin Disease (CAD)

1 Introduction

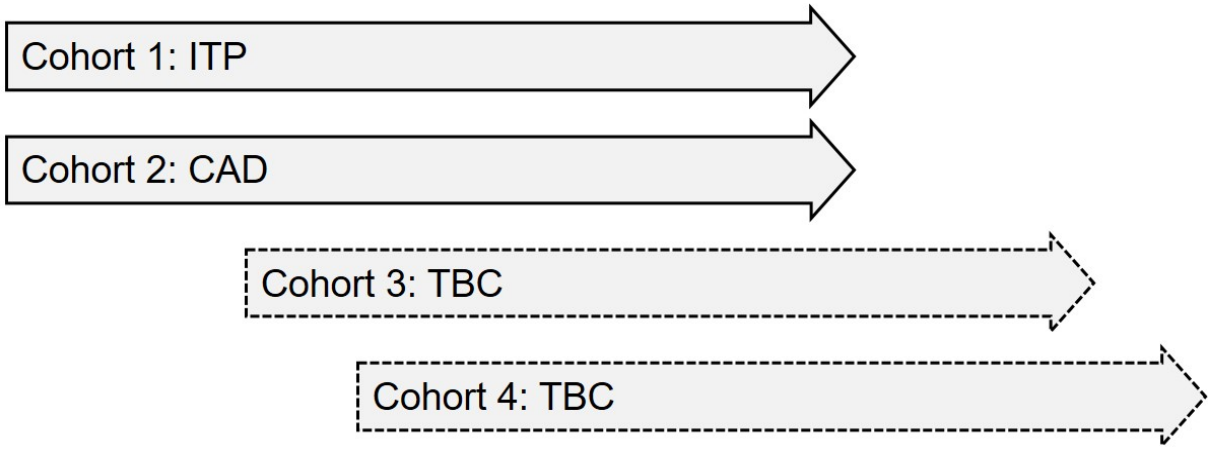
1.1 Background

Iptacopan (LNP023) is a novel, orally administered, low molecular-weight, first-in-class and selective inhibitor of complement factor B (FB), a key component of the complement alternative pathway (AP) C3 and C5 convertases. By inhibiting both AP C3 and C5 convertases, iptacopan blocks both AP-dependent C3 activation and membrane attack complex (MAC) formation (Schubart et al 2019). Iptacopan also blocks the amplification loop of the complement system, which, independently of the initiating trigger, is an important contributor to overall MAC formation *in vitro* (Harboe et al 2004). Importantly, iptacopan does not interfere with amplification-independent, direct activation initiated via the classical (CP) and lectin pathways (LP) – consequently, in immunized individuals, MAC-dependent killing of *Neisseria spp.* (for example) through activation of the CP is expected to be maintained.

In non-clinical studies, iptacopan has demonstrated a dose-dependent inhibition of the AP and a good safety profile (Schubart et al 2019, Mainolfi et al 2020). Inhibition of complement activation was confirmed in translational assays using samples from patients with paroxysmal nocturnal hemoglobinuria (PNH), C3 glomerulopathy (C3G) and atypical hemolytic uremic syndrome (aHUS) as well as in a rat model of glomerulonephritis (passive Heyman nephritis). The safety/tolerability and preliminary efficacy of iptacopan in humans is supported by data from three completed phase 1 studies in healthy volunteers and by emerging positive data from several phase 2 and 3 trials across different indications, including PNH (Risitano et al 2020), C3G, IgA nephropathy (IgAN), and idiopathic membranous nephropathy (iMN). For a more detailed overview of the non-clinical and clinical data on iptacopan to date, please refer to the Investigator's Brochure.

The encouraging efficacy and reassuring safety profile of iptacopan seen in early clinical trials involving patients with AP-driven diseases and the established role of the AP in the amplification loop have raised hope that AP inhibition with iptacopan could also benefit patients with autoantibody-mediated diseases with high CP-mediated complement activation. The aim of this proof-of-concept study is to assess the potential for iptacopan treatment in different autoantibody-mediated benign hematology disorders with evidence of complement activation in at least a subset of patients. The study is designed as a basket study (Figure 1-1) with two initial cohorts/indications, namely primary immune thrombocytopenia (ITP) and primary cold agglutinin disease (CAD). Further cohorts/indications, such as warm autoimmune hemolytic anemia (wAIHA) and/or thrombotic thrombocytopenic purpura (TTP), with similar study design and assessments, may be added via substantial protocol amendment.

Figure 1-1 Basket study design



1.1.1 Cohort 1: Immune thrombocytopenia (ITP)

Primary immune thrombocytopenia (ITP) is an autoimmune, mostly IgG-mediated thrombocytopenia, which usually presents acutely with signs and symptoms of bleeding in the absence of a specific underlying cause. Though considered a rare disease, with an annual incidence of 33/million in adults (50-100/million in children) and an estimated prevalence in the U.S. of 86,000, it is the most common autoimmune hematological disorder.

Standard of care for newly diagnosed primary ITP, beyond watchful waiting and supportive therapy, consists of corticosteroids, intravenous immunoglobulins (IVIG), or anti-Rho(D) immunoglobulin. However, most adults receiving these treatments will eventually relapse and require further therapy, with subsequent treatment options including thrombopoietin receptor agonists (TPO-RA), including eltrombopag, avatrombopag and romiplostim, as well as rituximab, fostamatinib, and splenectomy. Despite these options, there continues to be an unmet medical need, namely for therapies inducing durable remissions in relapsed / refractory patients and for targeted therapies with predictive biomarkers.

In terms of pathophysiology, whereas platelet destruction is thought to be primarily mediated in the spleen via antibody-dependent cellular cytotoxicity (ADCC), several lines of evidence indicate significant complement activation in at least a subset (roughly 30-50%) of ITP patients (Peerschke et al 2010; Cheloff et al 2020; Castelli et al 2020). Importantly, several complement component 1 (C1) inhibitors have recently shown preliminary efficacy in patients with refractory primary ITP (Roesch and Broome 2016; Broome et al 2020).

1.1.2 Cohort 2: Cold agglutinin disease (CAD)

Primary cold agglutinin disease (CAD) is an autoimmune hemolytic anemia, often triggered by cold temperatures or viral infections. Although the term “primary” implies the absence of a specific underlying cause, recent evidence suggests that the majority of patients actually have a low-grade lymphoproliferative disorder (Berentsen et al 2019). As a rare disease with an annual incidence of 1/million and an estimated prevalence in the U.S. of 5,000, primary CAD usually manifests acutely with signs and symptoms of hemolytic anemia and almost exclusively affects adults, with a median age of 67 years at presentation.

Standard of care for acute primary CAD, beyond watchful waiting and supportive therapy (including red blood cell transfusions), consists of plasmapheresis and/or intravenous immunoglobulins (IVIG). The main treatment option for refractory cases consists of rituximab, with or without bendamustine. Despite these options, there continues to be an unmet medical need, namely for therapies inducing durable remissions in relapsed / refractory patients and for targeted therapies with predictive biomarkers.

In terms of pathophysiology, hemolysis is triggered by cold-reacting autoantibodies (mostly IgM) targeting different red blood cell surface antigens, resulting in complement-dependent, extra- and intravascular hemolysis. Importantly, several complement inhibitors (eculizumab, sutimlimab) have shown preliminary benefit in patients with refractory primary CAD (Röth et al 2018; Jäger et al 2019; Röth et al 2021).

1.2 Purpose

The main purpose of this study is to evaluate the efficacy and safety of iptacopan in participants with autoimmune benign hematological disorders such as primary ITP and primary CAD.

2 Objectives, endpoints and estimands

Table 2-1 Objectives and related endpoints

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 • **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

Objective(s)	Endpoint(s)
• 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 in the respective target populations	• Iptacopan PK parameters including but not limited to Cmax, AUCtau, AUClast, Ctrough and Tmax.

[redacted]

2.1 Primary estimands

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 unique prior therapy administered with the intention to treat ITP (see Section 5).
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 unique prior therapy administered with the intention to treat CAD (see Section 5).
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.

2.2 Secondary estimands

Not applicable.

3 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. As outlined in Section 1.1, the study is set up as a basket study (Figure 1-1) to allow inclusion of new cohorts (=indications).

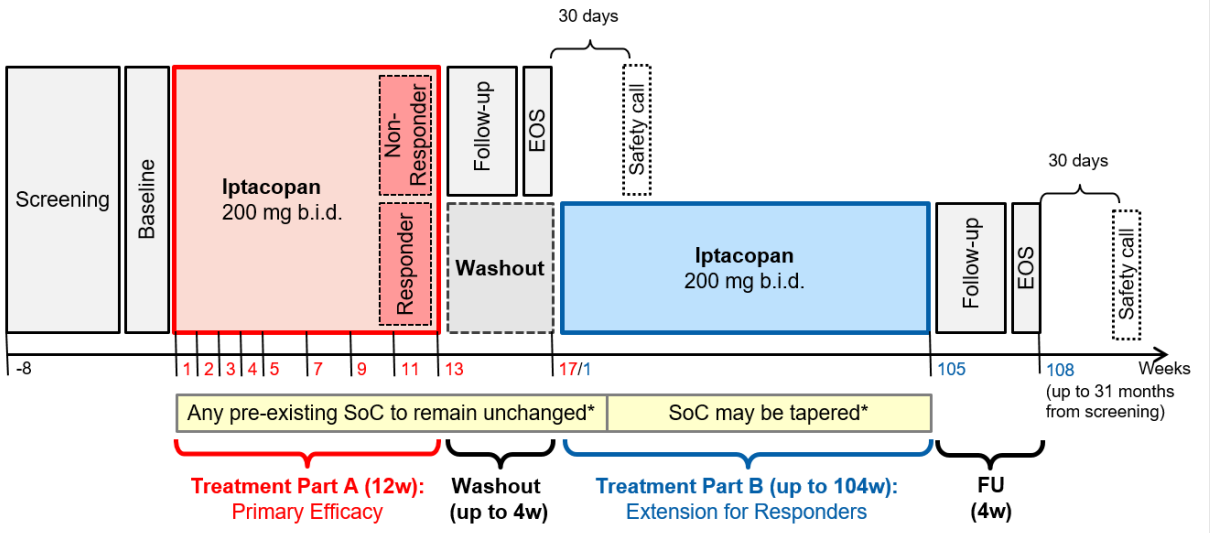
The study starts with two initial cohorts/indications and participants will be assigned to the relevant cohort based on their diagnosis:

- Cohort 1: participants diagnosed with primary ITP
- Cohort 2: participants diagnosed with primary CAD

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

The study design / participant journey is illustrated in Figure 3-1.

Figure 3-1 Study design



*SoC allowances vary between different cohorts

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). Participants meeting the primary endpoint (responders) will be offered to join Part B after a washout. In Part B, responders gain long-term access to iptacopan (24 months of treatment). The total study duration for responders will be up to 31 months (see Figure 3-1). Safety and efficacy assessments will be conducted at visits as specified in the Assessment Schedule (Table 8-1 and Table 8-3). Pharmacokinetic (PK) [redacted] samples will also be collected.

The study includes:

- **Screening/Baseline**: A screening period of up to 8 weeks to assess eligibility and vaccinate participants (see Section 6.2.1.2). Participants who meet the eligibility criteria at screening will move to baseline visit, where eligibility is confirmed and baseline evaluations are performed.
- **Treatment in Part A:** Part A includes a treatment period of 12 weeks (Day 1 to Day 85) with twice daily (b.i.d.) administration of 200 mg iptacopan. Any pre-existing background therapy (if allowed, see cohort-specific exclusion criteria in Section 5.2) must remain unchanged during Part A. Participants will have weekly visits for the first 4 weeks, followed by visits every 2 weeks for the latter 8 weeks. Safety and efficacy assessments will be conducted [redacted] at visits as specified in the Assessment Schedule for Part A (Table 8-1). There will also be two PK profiling days in Part A.
- **Follow-up/washout after Part A**: At the end of Part A, participants will be classified as responders or as non-responders based on whether or not they meet the cohort-specific primary endpoint (see Table 2-1 and Section 12.4.1) any time during Part A.
  - Non-responders (and responders not wanting to move on to Part B) will have a safety follow-up period of 4 weeks. Participants will undergo study completion evaluations and will complete the study during EOS visit approximately 4 weeks after the last study drug administration. All participants will have a follow-up call approximately 30 days after the last visit.
  - Responders will be offered to join the optional treatment extension in Part B. Prior to the start of Part B, all eligible participants will have a washout period lasting up to 4 weeks. After the washout period the participants will have the EOS Part A/Day 1 Part B visit. Participants reaching a critical safety cut-off level (as defined in the cohort-specific details in Section 3.1) at any follow-up/washout visit will have the opportunity to shorten the washout and move to EOS Part A/Day 1 Part B visit before completion of the 4 weeks of washout.
- **Treatment in Part B**: In Part B, iptacopan will be administered at 200 mg b.i.d. for up to 24 months. Any pre-existing background therapy (if allowed, see cohort-specific exclusion criteria in Section 5.2) may be tapered off earliest after 2 weeks of iptacopan treatment in Part B (see cohort-specific details in Section 3.1 for additional guidance). Assessments during Part B are described in the Assessment Schedule for Part B (Table 8-3). Notes:
  - Part B is optional, a responder may continue with Part B at the investigator`s or participant`s discretion. It is the investigator's responsibility to discuss all the available treatment options with the participant before the participant would enter into Part B. The discussion should be documented in the source document. If the participant is a responder but decides not to continue in Part B it should be documented in the electronic case report form (eCRF).
  - If a participant does not meet the primary endpoint but the investigator considers the response to be clinically meaningful and wants to continue with iptacopan treatment, the participation in Part B needs to be discussed and agreed with the Sponsor upfront on a case by case basis.

- **Follow-up after Part B**: After completion of the treatment period, the participants will move to a 4-week follow-up and complete the study at EOS for Part B. All participants will have a follow-up call approximately 30 days after the last visit.

3.1 Cohort specific details

3.1.1 Cohort 1: primary ITP

Approximately 20 participants diagnosed with primary ITP and sustained thrombocytopenia will be enrolled. Participants will be stratified based on complement activity (sC5b-9 levels) at screening in to one of two groups until approximately 10 participants have been assigned to each group:

- sC5b-9 high (≥ 200 ng/mL)
- sC5b-9 low (< 200 ng/mL)

Depending on the distribution of baseline sC5b-9 levels amongst the first 10 enrolled participants, the threshold of 200 ng/mL may be modified (e.g., if most participants are below or above).

Washout period cut-off: If during the washout period for responders the platelet count drops to <30 k/μL and/or the participant experiences a bleeding episode, the participant will be allowed to skip the remaining follow-up visits and move directly to EOS Part A/Day 1 Part B.

Tapering of pre-existing background therapy in Part B: Participants on pre-existing, background either TPO-RA or low-dose corticosteroid therapy will be allowed to taper and eventually discontinue this therapy starting earliest after 2 weeks of iptacopan therapy in Part B, as long as the platelet count is and remains ≥50 k/μL. Tapering may be done per the investigator's discretion, taking into account the respective label as well as standard practice and/or current literature guidance (such as Cuker et al 2020 for TPO-RA). Given the risk of rebound thrombocytopenia, it is not recommended to discontinue TPO-RA therapy without tapering, and additional platelet count monitoring is recommended during tapering.

3.1.2 Cohort 2: primary CAD

Approximately 10 participants diagnosed with primary CAD and sustained anemia and evidence of ongoing hemolysis will be enrolled.

Washout period cut-off: If during the washout period for responders the hemoglobin level drops to <10 g/dL, the participant will be allowed to skip the remaining follow-up visits and move directly to EOS Part A/Day 1 Part B.

3.1.3 Cohort 3

Placeholder for a potential 3rd Cohort. Additional details will be provided in a substantial protocol amendment.

3.1.4 Cohort 4

Placeholder for a potential 4th Cohort. Additional details will be provided in a substantial protocol amendment.

3.2 Off-site Procedures

At the investigator's direction and based on benefit-risk considerations of the participant's clinical condition, qualifying participants may be offered the option to have certain clinical trial procedures performed at an off-site location, as defined in Section 8. A hybrid model is planned for this study, incorporating both onsite and off-site visits. The off-site procedures will be offered in certain countries and sites as determined by Novartis based on national and local regulations. Participants have the option of participating in one or more off-site visits, based on participant preference and investigator discretion.

One or more of the following elements may be implemented to support off-site visits where allowed by national and local regulations:

- Telemedicine
- Off-site healthcare professionals (OHP)
- Direct-to-participant shipment of study supplies
- Direct-to-participant shipment of study treatment (refer to Section 6)
- Electronic Source (eSource) Direct Data Capture (DDC)

Off-site procedures are not applicable to Cohort 2 because CAD blood samples require incubation at 37-39°C immediately upon collection until further processing and/or analysis to minimize the risk of spontaneous *in vitro* RBC agglutination. This cannot be supported at off-site locations, nor during transportation to the analyzing lab.

3.2.1 Responsibility of Investigators

Procedures that are performed off-site remain under the oversight of the investigator, who retains accountability for the conduct of all safety and efficacy assessments delegated to an OHP, and will ensure the rights, safety and wellbeing of participants. This includes ensuring the following (including, but not limited to):

- the identification, management and reporting of adverse events (AEs) and serious adverse events (SAEs) are performed in accordance with the protocol and applicable regulations
- OHPs have appropriate qualifications, training, and experience to successfully conduct off-site procedures
- source data collected off-site are reviewed and evaluated in a timely manner
- the investigator or delegate is available to be contacted by the OHP if any issues or concerns are noted during an off-site visit
- where relevant, the investigator or delegate will be present via telemedicine for a portion of the off-site visit to support the physical examination

3.2.2 Responsibility of OHPs

OHPs must have the required qualifications, training, and experience to conduct off-site assessments. OHPs are responsible to conduct delegated assessments and collect relevant data at off-site visits in accordance with the clinical trial protocol, International Conference for Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and national and local regulations and guidelines.

The OHPs will be provided by a third-party vendor sourced by Novartis. Where a site wishes to use OHPs that are not provided by Novartis this must be agreed with Novartis before use.

Any issues or safety concerns identified by the OHP will be promptly communicated to the investigator or delegate according to a pre-defined communication plan.

3.2.3 Telemedicine

Telemedicine is optional and subject to local and national regulations (see Section 3.2). The sponsor has qualified and contracted a third-party vendor to provide telemedicine platform technology for this study. The selected platform is a validated system complying with relevant ICH E6 GCP guidelines. Trial participants can interact with site personnel using online communication tools built into the platform, enabling the following capabilities:

- Secure videoconferencing which allows the participant, OHP and site personnel to be connected
- Reminders to be automatically sent to participants (e.g. visit or dosing compliance)
- eSource Direct Data Capture (DDC) (see Section 3.2.4)

3.2.4 Data Flow

The OHPs will enter data at off-site visits into electronic source documentation forms contained in an eSource DDC platform, which has been validated for use in clinical research. Where paper source documentation exists, images of documentation will be uploaded electronically into the same platform as certified copies, and the original documentation will then be sent to the trial site.

Data contained in the platform are available to site and sponsor staff based on role-based access and permissions, and will be stored in a robust and secure cloud-based back-end environment. Only sponsor staff who are responsible for field monitoring activities will have access to the source data, which may include some personally identifiable information, consistent with the access that is provided to a field monitor in a traditional onsite clinical trial model.

Relevant data in the eSource DDC platform may be manually transcribed by site staff into the study electronic data capture (EDC) system. Alternatively, the platform allows for configuration that enables data to be automatically exported into the study EDC system.

Certified copies of data in the eSource DDC platform will be provided to investigator and/or site personnel, and promptly and regularly uploaded into the participant's medical records, according to local guidelines.

Investigators will have continuous, near real time access to assigned studies and all participant records within their studies in the eSource DDC platform, with the ability to add, edit, review and sign forms within participant records.

The platform maintains a secure, GCP-compliant audit trail and uses measures such as encryption and access controls to ensure that data privacy and security is maintained. Additional details will be contained in a separate Site Manual.

4 Rationale

4.1 Rationale for study design

Table 4-1 Rationale for study design

Study Design Aspect	Rationale
Basket	The basket design allows for incorporation of additional benign hematology indications with high unmet medical need, such as wAIHA and/or TTP. This will result in an improved and more efficient inclusion of participants. In addition, since patients with the initial (i.e., ITP, CAD) and potential further indications (e.g., wAIHA, TTP) are expected to visit the same investigators/sites, and considering the shared study design and similar assessments across the indications, the basket study design is expected to reduce the operational burden for the participating sites.
Open-label, single-arm	The open-label, single-arm design of this non-confirmatory study will allow all participants to receive iptacopan in rare indications with unmet medical need. The primary endpoint is a lab parameter with low potential for bias, and the underlying/spontaneous response rate (in the absence of rescue therapy) in these refractory patient populations is expected to be negligible (e.g., Jurczak et al 2018, Bussel et al 2014).
Vaccines/prophylactic antibiotics	To reduce the risk of *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* infections, all participants will either be vaccinated prior to first treatment with iptacopan or, if not vaccinated adequately, receive prophylactic antibiotic treatment. The study will include a longer screening period to allow time to assure development of protective immunity after vaccinations. In addition, prophylactic antibiotics are mandatory throughout study Part A for all participants with prior splenectomy.
Duration of study periods	Part A: 12 weeks of treatment are expected to be sufficient to detect responses and also assess if response can be sustained for several weeks. Part B: The 24-month treatment duration will allow the participants to have prolonged access to iptacopan treatment and additional long-term safety data can be collected in the proposed study populations.
Washout prior to Part B	The study includes a study drug washout after Part A, followed by a re-start in Part B, to further strengthen any evidence and specificity of efficacy seen in Part A. Participants with lab parameters worsening during washout are allowed to shorten washout time to minimize participant burden.
Part B	The purpose of Part B is to offer responders prolonged access to iptacopan treatment and collect additional long-term safety and efficacy data.
Stratification (Cohort 1 only)	Since only a subset of primary ITP patients (roughly 30-50%) has evidence of complement activation (Peerschke et al 2010; Cheloff et al 2020; Castelli et al 2020), the assignment of ITP participants into 2 subgroups based on complement activation (sC5b-9) at screening should ensure that the sample size for both subgroups is sufficient to assess the impact of complement

Study Design Aspect	Rationale
	activation on the response to iptacopan treatment. The threshold was selected based on publically available and Novartis-internal data in both healthy volunteers and ITP patients. Since hemolysis is known to be largely complement-mediated in CAD, no stratification is deemed necessary for this cohort.

4.1.1 Rationale for choice of background therapy

In principle, the purpose of this study is to evaluate the potential of iptacopan monotherapy in the selected indications. However, taking into account standard-of-care practices, for Cohort 1 (primary ITP) only, participants may receive a concomitant therapy with either a thrombopoietin receptor agonist (TPO-RA) or low-dose corticosteroid, as long as it has been stable for at least 4 weeks prior to first iptacopan dose. The impact of this on the primary and secondary endpoints should be minimal as participants are required to have sustained thrombocytopenia at baseline irrespectively. No further background therapy directed against the indication under study is permitted (see Section 6.2.2 for further details).

4.1.2 Rationale for off-site visits

Off-site procedures are planned in this study to minimize burden on participants, and offer them increased flexibility to participate in the study from an off-site location (as described in Section 3.2 and defined in Section 8). This has the potential to broaden access to clinical trials for both participants and investigators. The hybrid approach will allow participants to maintain contact with the investigator, both face-to-face during clinic visits at site and through the telemedicine platform during off-site participation.

The scope of off-site procedures was determined based on a thorough operational feasibility review of the assessment schedule to assure comparability with onsite assessments, together with consideration of participant safety.

Off-site procedures do not apply to Cohort 2 because blood sample handling requires special attention to avoid spontaneous *in vitro* RBC agglutination.

4.2 Rationale for dose/regimen and duration of treatment

Iptacopan has been investigated in several renal (IgAN, C3G) and non-renal (PNH) indications. Based on exposure-response modelling, the 200 mg b.i.d. dose regimen was selected as the highest pharmacological dose, but doses down to 10 mg b.i.d. have been investigated. Clinical phase 2 data showed that, in all these indications (PNH, IgAN, C3G), the 200 mg b.i.d. dose regimen provided the highest response rate without any major safety concerns, and this was also supported by PKPD modelling and target occupancy data collected in these studies (see Investigator's Brochure). Consequently, 200 mg b.i.d. was selected for this study.

4.3 Rationale for choice of control drugs (comparator/placebo)

Not applicable.

4.4 Purpose and timing of interim analyses/design adaptations

Interim Analyses (IA)

Data from different cohorts will be analyzed separately. Database freezes/data cleanings may be combined for operational reasons if last data included in the IA is generated at similar timepoints (within same cohort or across different cohorts). The following IAs are planned for each cohort:

- A first IA 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.
- A second IA 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.

Additional information is presented in the interim analysis Section 12.7.

Design adaptations

This basket study will allow for inclusion of new cohorts as described in Section 3, via submission of subsequent substantial protocol amendments.

4.5 Risks and benefits

Based on the evidence of complement activation and its role in disease pathogenesis, as well as the early efficacy reported with several complement inhibitors, including the C1s inhibitor sutimlimab (see Section 1.1) (Broome et al 2020, Röth et al 2021), there is reason to believe that at least a subset of patients with either primary ITP or primary CAD, particularly those refractory to standard-of-care treatments, may benefit from complement inhibition with iptacopan. However, since iptacopan has not been studied in these indications, no conclusive statement regarding the efficacy of iptacopan in either ITP or CAD can be made.

The risks associated with the use of iptacopan are those inferred by its pharmacology and the results of preclinical safety studies. The most relevant risks are described below and a complete description of preclinical safety findings is available in the Investigator's Brochure. The risks will be minimized by adherence to the eligibility criteria, close clinical monitoring, early stopping rules, periodic review of the safety data, and guidance for the investigators in the Investigator's Brochure.

Based on their mechanism of action, the main risk of complement inhibitors is that of infections with encapsulated bacteria, in particular with *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*. However, translational research has shown that the serological response to meningococcal infection, while markedly reduced after classical pathway (CP) blockade with anti-C5 inhibitors like eculizumab, is maintained during AP blockade – bactericidal activity studies of serum from vaccinated patients against meningococci

showed that C5 inhibitors block killing of meningococci, whereas AP inhibitors have less inhibitory effect (Konar and Granoff 2017).

To date, while no infections were reported in pre-clinical studies with iptacopan, a single infection with encapsulated bacteria has been reported in clinical trials. The affected patient, with C3 glomerulopathy and a history of kidney transplantation, experienced acute respiratory distress syndrome with pneumococcal pneumonia and septic shock 11 months after starting treatment with iptacopan 200 mg b.i.d., while also receiving multiple concomitant immunosuppressants. The mitigation strategy to reduce the risk of infections includes vaccination against *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* according to local guidelines and availabilities, antibiotic prophylaxis where indicated (particularly for participants with additional immunosuppression such as prior splenectomy), close monitoring of signs and symptoms of infection, and prompt triaging, workup and treatment in case of any suspected infection. With this, the risk of serious infection during iptacopan treatment is considered to be low. Of note, there is a potential for vaccinations to worsen thrombocytopenia in patients with ITP and hemolysis in patients with CAD, however, the benefit of vaccination is thought to outweigh this risk.

Other safety risks, including the potential risks of testicular effects, bone marrow toxicity with severe anemia, aorta mineralisation and increased heart weight, as well as thyroid effects, are based on preclinical data, with no relevant findings in clinical studies performed to date. They will be assessed through regular monitoring of reproductive hormone levels, of hematological parameters, of heart rate and blood pressure, of thyroid hormone levels and of respective adverse events. Please refer to the Investigator's Brochure for more detailed information regarding these potential risks.

Safety results from the completed healthy volunteer studies and ongoing clinical trials in paroxysmal nocturnal hemoglobinuria (PNH) and several complement-driven renal diseases show iptacopan to be overall well tolerated and safe. In particular, no additional safety risks have been identified based on this early clinical data. More detailed information is available in the Investigator's Brochure.

Iptacopan did not show any mutagenic, teratogenic or genotoxic potential in completed standard battery of genotoxicity testing. In addition, iptacopan was tested in embryo-fetal development studies in rats and rabbits and no iptacopan-related adverse fetal findings were detected in any of the studies. However, iptacopan has not been used in pregnant women, therefore, women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria (Section 5.2). If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

No invasive procedures are planned as part of this study, with the exception of blood draws.

In summary, the risk-benefit relationship for treatment of primary ITP and primary CAD patients with iptacopan is positive, supporting the start of this study.

Risks related to off-site visits

Participants are not anticipated to be exposed to greater risks when participating in off-site assessments. OHPs will perform assessments according to the same processes and instructions defined in the protocol and study manuals for onsite visits wherever possible, thus data integrity is also expected to be comparable to onsite assessments. Safety management in an off-site setting will adhere to the same quality standards as for the traditional onsite model and remains under the responsibility of the investigator (refer to Section 3.2.1).

4.5.1 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected over a period of 6 months (Part A) or 25 months (Part B), from each participant as part of the study. The approximate volumes are mentioned in the ICF. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the Assessment Schedule (Table 8-1 and Table 8-3).

A summary blood log is provided in the laboratory manual. Instructions for sample collection, processing, storage and shipment are also available in the laboratory manual.

See Section 8.5.3.2 on the potential use of residual samples.

4.6 Rationale for Public Health Emergency mitigation procedures

In addition to the planned off-site procedures, in the event of a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, additional mitigation procedures to ensure participant safety and trial integrity may be implemented. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by Off-site Health Professionals (OHP) to the participant´s home, can replace on-site study visits (in addition to the already planned off-site visits), for the duration of the disruption until it is safe for the participant to visit the site again.

Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Study Population

The study population will comprise a total of approximately 30 enrolled participants:

- Cohort 1: Approximately 20 participants with primary ITP will be enrolled; approximately 10 participants each with high and low complement activity, respectively.
- Cohort 2: Approximately 10 participants with primary CAD will be enrolled.

Participants may be replaced if they discontinue treatment early (for any reasons other than safety, see Section 6.4.2.1). See Section 8.1 for more details on screening and re-screening.

Each inclusion and exclusion criterion specifies whether the criterion should be assessed at screening and/or baseline. Pre-dose assessments on Day 1 are not considered for study eligibility. A relevant record (e.g., checklist) of the eligibility criteria must be stored with the source documentation at the study site.

5.1 Inclusion criteria

Participants eligible for inclusion in any cohort of this study must meet **all** of the following criteria. In addition, participants must meet the cohort-specific criteria specified in the relevant subsections below.

1. Written informed consent must be obtained before any assessment is performed.
2. Able to communicate well with the investigator, to understand and comply with the requirements of the study.
3. Vaccination against *Neisseria meningitidis* and *Streptococcus pneumoniae* infections is required prior to the start of treatment. If the patient has not been previously vaccinated, or if a booster is required, the vaccine(s) should be given according to local regulations, at least 2 weeks prior to first dosing. If treatment has to start earlier than 2 weeks post vaccination, prophylactic antibiotic treatment must be initiated.
4. If not received previously, or if a booster is required, vaccination against *Haemophilus influenzae* infection should be given, if available and according to local regulations, at least 2 weeks prior to first dosing.
5. Weight of at least 35 kg and body mass index (BMI) of at least 15 kg/m2.

5.1.1 Cohort 1 specific inclusion criteria

101. Male and female participants aged ≥18 years at baseline with a diagnosis of persistent or chronic primary ITP (diagnosed at least 3 months prior to baseline).

102. Participants must have received at least 1 unique prior therapy, defined as any pharmaceutical agent or type of non-pharmacological intervention (e.g., splenectomy) administered with the intention to treat ITP. Transfusions of blood products are not accounted as prior therapies. For South Korea, participants must have received at least 2 unique prior therapies to treat ITP, unless they do not qualify for available treatment options per the investigator's assessment.

103. Sustained thrombocytopenia (platelets <30 k/µL), as documented at baseline plus in ≥2 additional assessments separated by at least 1 week in the prior 3 months.

5.1.2 Cohort 2 specific inclusion criteria

201. Male and female participants aged ≥18 years at baseline with a diagnosis of primary CAD, including CAD arising in the setting of a low-grade lymphoproliferative disorder a) not requiring any therapy and b) without evidence of diffuse lymphadenopathy (lymph nodes at multiple stations measuring >2 cm) or of significant hepatosplenomegaly, i.e., the liver edge should be <5cm and the spleen <3 cm below the costal margin on physical examination, or, if the size has been determined radiographically (imaging is not required for eligibility), the craniocaudal dimension should be <18 cm for each organ.

202. Positive direct antiglobulin test for C3d only (or predominantly) and cold agglutinin titer of ≥64 at 4°C at screening or documented in the prior 3 months.
203. Laboratory evidence of ongoing hemolysis (LDH or total bilirubin above ULN) at baseline.
204. Sustained anemia (Hb <10 g/dL), as documented at baseline plus in ≥2 additional assessments separated by at least 1 week in the prior 3 months.
205. Participants must have received at least 1 unique prior therapy, defined as any pharmaceutical agent or type of non-pharmacological intervention (e.g., plasmapheresis) administered with the intention to treat CAD. Transfusions of blood products are not accounted as prior therapies.

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study. Additional cohort-specific exclusion criteria are listed in the relevant subsections and apply only to the specific cohort.

1. History of hypersensitivity to any of the study treatments or excipients or to drugs of similar chemical classes.
2. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 30 days, whichever is longer; or longer if required by local regulations.
3. Past or concomitant use of medications prohibited by the protocol (see Section 6.2.2 (Prohibited medication) or Table 6-2 (Prohibited medications)).
4. Known or suspected hereditary or acquired complement deficiency.
5. History of primary or secondary immunodeficiency, including a positive HIV test result.
6. Chronic infection with Hepatitis B (HBV) or Hepatitis C (HCV). A positive HBV surface antigen (HBsAg) test, or if standard local practice, a positive HBV core antigen test, excludes a participant. Participants with a positive HCV antibody test must have HCV RNA levels measured. Participants with positive (detectable) HCV RNA must be excluded. See also Table 8-4.
7. History of recurrent invasive infections caused by encapsulated organisms, including *N. meningitidis*, *S. pneumoniae*, or *H. influenzae*.
8. Presence or suspicion (based on judgment of the investigator) of any active infection within 14 days prior to first study drug administration.
9. Any medical condition deemed likely to interfere with the patient's participation in the study.
10. Severe concurrent co-morbidities including but not limited to patients with severe kidney disease (CKD stage 4, dialysis), advanced cardiac disease (NYHA class IV) or severe pulmonary disease (e.g., severe pulmonary hypertension (WHO class IV)) , as judged by the investigator, both at screening and baseline.
11. Any malignant disease diagnosed within 5 years of screening, with the exception of localized non-melanoma skin cancer, *in situ* cervical cancer, or, for CAD, a low-grade lymphoproliferative disorder (see Section 5.1.2).

12. History of bone marrow/hematopoietic stem cell or solid organ transplantation.
13. Thromboembolic event within 3 months prior to baseline.
14. Ongoing drug or alcohol abuse that could interfere with patient's participation in the trial.
15. Female participants who are pregnant or breastfeeding, or intending to conceive during the course of the study.
16. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of investigational drug and for 1 week after last iptacopan dose. *Effective contraception methods include:*
    - Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant.
    - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For UK: with spermicidal foam/gel/film/cream/vaginal suppository
    - Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS)

    In case of use of oral contraception women should be stable on the same pill for a minimum of 3 months before taking study drug.

    If local regulations deviate from the contraception methods listed above and require more extensive measures to prevent pregnancy, local regulations apply and will be described in the ICF.

    Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms). Women are considered not of child bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential. Refer to Section 8.4.3 (Pregnancy and Assessments of Fertility).

17. Patients with any active severe bleeding or history of intracranial hemorrhage within last 12 months.
18. Liver disease, or liver injury as indicated by abnormal liver function tests at Screening:
    - Any single parameter of ALT, AST, GGT, alkaline phosphatase must not exceed 2.5x upper limit of normal (ULN). For Cohort 2 CAD participants, AST levels up to 5xULN are acceptable if attributed to ongoing hemolysis alone.
19. Unstable medical condition as judged by the investigator at Screening, including but not limited to myocardial ischemia or unstable thrombotic event.
20. Patients with estimated GFR (using the CKD-EPI formula) <45 mL/min/1.73 m^2 at screening
21. History of clinically significant ECG abnormalities, or any of the following ECG abnormalities at screening or baseline visit:
    - QTcF >450 msec (males)
    - QTcF >460 msec (females)
    - History of familial long QT syndrome or known family history of Torsades de Pointes
    - Use of agents known to prolong the QT interval unless they can be permanently discontinued for the duration of the study
22. Sitting vital signs as follows at time of baseline visit:
    - Body temperature persistently <35.0 or >37.5 ºC
    - Systolic blood pressure <90 or >180 mm Hg
    - Diastolic blood pressure <50 or >110 mm Hg
    - Resting pulse rate <50 or >90 bpm.

    Below 50 bpm is acceptable, if no other clinically significant ECG abnormalities as per investigator decision. For subjects with heart rates less than 50 bpm, evidence should be provided that they have no history of a) moderate or severe valvular disease; b) history of coronary artery disease, myocardial infarction, hypertension or diabetes mellitus; c) history of cardiomyopathy, congenital heart defect, open heart surgery, or ongoing arrhythmia; d) family history of sudden death in a first degree relative

5.2.1 Cohort 1 specific exclusion criteria

101. Secondary ITP, as may arise in the setting of certain autoimmune disorders, immunodeficiency syndromes, infections, malignancies, and drug treatments.
102. 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.
103. Abnormal coagulation screening labs (PT/INR, PTT).

5.2.2 Cohort 2 specific exclusion criteria

201. Secondary cold agglutinin syndrome, as may arise in the setting of certain infections, autoimmune disorders, and malignancies (with the exception of a low-grade lymphoproliferative disorder, see Section 5.1.2).

202. No CAD-directed background therapy permitted.

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Please see Table 6-1 for details on investigational drug. No control drugs will be used in this study.

Table 6-1 Investigational drug

Investigational Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)
Iptacopan (LNP023) 200 mg	Capsule	Oral use	Open label participant specific supplies	Novartis

6.1.2 Additional study treatments

No additional treatment beyond investigational drug are included in this trial.

6.1.3 Treatment arms/group

There is only one treatment arm per cohort. All participants will be assigned at Day 1 visit to the treatment arm of iptacopan 200 mg b.i.d. for 12 weeks (Part A).

Responders (as defined by the primary endpoint) and potentially non-responders with a clinically meaningful response (see Section 3) may join the treatment extension part after a washout period to receive iptacopan 200 mg b.i.d. for up to 24 months (Part B).

6.1.4 Post Trial Access

Responders will be offered extended access to iptacopan during the extension part of this study (Part B) for up to an additional 24 months beyond the main treatment part (Part A). Beyond this, responders may benefit from post trial access based on local regulations.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate Case Report Forms.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before enrolling a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Iptacopan has multiple disposition pathways of which oxidative metabolism by CYP2C8 is the most prominent. Iptacopan is not a potent inhibitor of metabolic enzymes or transporters. However, an inhibition of P-glycoprotein (P-gp) at the intestinal level cannot be excluded. Iptacopan is also not a potent inducer, indicating that iptacopan can be safely co-administered with oral contraceptives. Until completion of the full assessment of potential drug-drug interactions in the currently ongoing clinical DDI study CLNP023A2104, some concomitant medications are either prohibited (see Section 6.2.2) or should be used with caution.

Iptacopan has been shown to have a weak inhibition potential for the liver uptake transporter OATP1B1. Calculation revealed that the exposure (AUC) of respective sensitive substrates may be increased by <1.5 fold. Although the expected effect on the exposure of respective co-medications is small and may not be clinically relevant, it is recommended to combine iptacopan with sensitive OATP1B1 substrates or those having a narrow therapeutic index with caution. A list of OATP1B1 substrates to be used with caution may be provided to the investigators upon request.

Iptacopan has also been shown to inhibit the efflux transporter P-gp on the intestinal level but not the liver. Therefore, the direct oral anti-coagulation drugs apixaban, rivaroxaban and edoxaban which are P-gp substrates should be used with caution. For edoxaban a staggered dosing (see below) is recommended, in particular for participants with impaired kidney function.

Unless prohibited for other reasons (see Section 6.2.2), for narrow therapeutic index (NTI) drugs (e.g., digoxin, fentanyl, phenytoin, quinidine, tolvaptan) which are substrates for the efflux transporter P-gp with no alternative treatment available, a staggered dosing approach is recommended. This can be accomplished by administering the respective co-medication >3 hours following oral administration of iptacopan. Alternatively, compounds with a short Tmax of around < 2 hours (i.e., fast absorption) may be given >1 hour prior to iptacopan. The staggered dosing will avoid increases in systemic exposure of co-administered drugs due to P-gp inhibition by iptacopan at the intestinal level. For participants receiving immunosuppressants (stable dose) and if their exposure is no longer monitored, it is advisable to resume therapeutic drug monitoring after start of treatment with iptacopan (single assessment).

6.2.1.2 Vaccinations

Required/recommended vaccinations should be completed as per inclusion criteria defined in Section 5.1. These vaccines should cover as many serotypes as possible (including meningococcal serotypes A, C, Y, W-135 and B). To minimize participant burden, the use of multivalent vaccines is recommended as locally available and per local guidelines and regulations (e.g., quadrivalent vaccine for *N. meningitidis* which covers serotypes A, C, Y and W-135; and Pneumovax-23 which covers 23 *S. pneumoniae* serotypes). For the vaccination type and booster requirements use local guidelines, and locally available vaccines (and refer to the package insert of those or local guidelines). The screening period may be extended to allow vaccination procedures to be completed, in case of multiple vaccination needs and local/country requirements. This is applicable for vaccinations only, while all the other screening assessments must be performed as indicated in the Assessment Schedule Table 8-1. Vaccinations should be started at the earliest possible to avoid extension of screening period.

Other vaccinations, including COVID-19 vaccination, should preferably be given prior to enrollment, but, if indicated, they may be given during the course of the study as well, with the exception of live vaccinations, which are prohibited as per Table 6-2. Based on pre-clinical data, iptacopan is not expected to interfere with the antibody response to vaccination. All vaccinations should be recorded in eCRF.

6.2.1.3 Prophylactic antibiotic treatment

Antibiotic prophylaxis per local standard of care is mandatory throughout the entire main treatment period (Part A) for any participant with a prior history of splenectomy; the decision to maintain or discontinue antibiotic prophylaxis during the extension (Part B) may be made by the investigator on a case-by-case basis. In addition, antibiotic prophylaxis should be initiated in case iptacopan treatment is started earlier than 2 weeks post-vaccination for *N. meningitides* and *S. pneumoniae*.

For treatment of suspected infections, see Section 6.7.2.

6.2.2 Prohibited medication

Use of the treatments displayed in the below table are not allowed.

Table 6-2 Prohibited medication

Medication	Prohibition period	Action taken
Complement inhibitor therapy other than iptacopan	Any time prior to enrollment until EOS	Discontinue study treatment
Targeted B-lymphocyte depleting therapy (incl. rituximab)	3 months prior to first iptacopan dose until EOS	Discontinue study treatment
Systemic corticosteroids	2 weeks prior to first iptacopan dose until EOS. Exceptions: Rescue therapy from Day 1 onwards (see Section 6.2.3) or one-time prophylaxis for hypersensitivity	Discontinue study treatment, unless covered by exceptions.

Medication	Prohibition period	Action taken
	reactions. In addition, for participants with ITP, low-dose corticosteroids (prednisone-equivalent of ≤10 mg daily) are allowed as long as dosage stable for at least 4 weeks prior to first iptacopan dose.	
Other immunosuppressive or antineoplastic agents, including but not limited to anti-Rho(D) IG, bendamustine, bortezomib, cyclosporine, cyclophosphamide, IVIG, mycophenolate mofetil, vincristine	1 month prior to first iptacopan dose until EOS. Exception: Rescue therapy from Day 1 onwards (see Section 6.2.3).	Discontinue study treatment, unless covered by exception
Other regimens to treat the primary indication	2 weeks prior to first iptacopan dose until EOS. Exceptions: Thrombopoietin receptor agonists (TPO-RAs) (single agent allowed for ITP participants only as long as stable dosage for at least 4 weeks prior to first iptacopan dose).	Discontinue study treatment, unless covered by exceptions
Anti-thrombotic or anti-platelet therapy	Prohibited for ITP Cohort 1 only: 2 weeks prior to first iptacopan dose until EOS.	Discontinue study treatment, unless covered by exception
Live vaccines	Prohibited for the entire study treatment duration	
Gemfibrozil	Gemfibrozil must be interrupted at least 48 hours before first iptacopan dose until end of iptacopan treatment (and replaced with another appropriate medication used for that indication)	
Strong inhibitors of CYP2C8 such as clopidogrel	Strong inhibitors of CYP2C8 must be interrupted 7 days before first iptacopan dose until end of iptacopan treatment (and replaced with another appropriate medication used for that indication)	
“Sensitive substrates” for the efflux transporter P-gp or P-gp substrates with narrow therapeutic index (NTI) (e.g., digoxin, fentanyl, phenytoin, quinidine, tolvaptan)	Medication to be interrupted 12 hours before first iptacopan dose. Exception: if staggered dosing can be applied (see Section 6.2.1.1)	

6.2.3 Rescue medication

Rescue therapy, if indicated, may be initiated at the investigator's discretion.

However, if rescue therapy is given during the screening period, i.e., prior to the start of iptacopan treatment on Day 1, the prohibition period as defined in Table 6-2 must still be followed. Consequently, the start of the treatment period (Day 1) may need to be shifted and any affected assessments at screening or baseline may need to be repeated accordingly. Importantly, in case a transfusion of blood products is necessary during the screening period, treatment start must not occur earlier than 7 days following the transfusion and any affected assessments may need to be repeated accordingly.

From Day 1 onwards, if there is need to use rescue therapy before response criteria are met, the participants will be treated as non-responders. Conversely, use of rescue therapy after the primary endpoint is met, does not impact the response status with respect to that endpoint.

- For ITP (Cohort 1), rescue therapy generally consists of corticosteroids, intravenous immunoglobulins (IVIG) or anti-Rho(D) immunoglobulin and may be indicated in case of worsening thrombocytopenia and/or signs or symptoms of bleeding.
- For CAD (Cohort 2), rescue therapy generally consists of plasmapheresis, IVIG and/or red blood cell transfusions and may be indicated in case of worsening anemia and/or critical hemolysis.

6.2.4 Restriction for study participants

For the duration of the study, participants should be informed and reminded of the restrictions outlined:

- Contraception requirements as listed in Section 5.2
- Prohibited medications as listed in Section 6.2.2

6.2.4.1 Dietary restrictions and smoking

There are no specific dietary restrictions.

6.2.4.2 Other restrictions

Not applicable.

6.3 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described in Section 6.1.1.

A unique medication number is printed on the study medication label.

As per the treatment assigned to the participant, investigator staff will select the study treatment to dispense to the participant. The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the package to the participant, site personnel will detach the outer part of the label from the package and affix it to the participant's source document.

On each study visit (including on-site visits and potential home nursing visits), investigator staff should ensure that the IMP is stored appropriately in the participant's home and that the participant is taking the IMP in compliance with the study requirements (see in Section 6.3.2).

Where delivery of IMP directly to a participant's secure off-site location (e.g. home) is permitted by national and local governing regulations then dispatch of IMP from either the site, or a pharmacy, to the participant will be performed under the accountability of the Investigator. In case IMP is couriered from a pharmacy, site personnel will contact the pharmacy for dispensing and the 2-part label will not be utilized. The provisioning of supply will be for a maximum of 8 weeks supply. In this case, regular contacts will occur between the site and the participant for instructional purposes, safety monitoring, investigation of any adverse events, ensuring participants continue to benefit from treatment, and discussion of the participant's health status until the participants can resume visits at the study site.

In the US, study treatment and all required clinical study supplies may be distributed direct to the participant utilizing an extension of the IND for compliance purposes.

6.3.1 Handling of study treatment and other treatment

6.3.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by field monitors during site or remote monitoring visits, and at the completion of the trial.

The treatment for off-site administration will be handled and shipped in line with the protocol and required procedures for shipping.

If study treatment is administered at home e.g. oral medication, participants will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

The site may destroy and document destruction of unused study treatment, drug labels and packaging as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.3.2 Instruction for prescribing and taking study treatment

- Participants should take 200 mg iptacopan b.i.d. orally at approximately the same time each day in the morning and approximately 12 hours later in the evening (total daily dose of 400 mg). Each dose consists of 1 capsule of 200 mg.
- The first dose should be administered on site. On days that PK samples are obtained, the participant should take iptacopan after the pre-dose PK samples and prior to post-dose PK samples, when instructed by the study staff.
- Participants may take iptacopan without regard to food. Each dose may be taken with a glass of water.
- Participants should be instructed to swallow whole capsules and not to chew or open them
- If vomiting occurs during the course of treatment, participants should not take the iptacopan again before the next scheduled dose.
- Participants should be instructed not to make up missed doses. A missed dose is defined as a case when the full dose is not taken within 4 hours after the approximate time of the usually daily dosing. That day's dose should be omitted and the participant should continue treatment with the next scheduled dose.

6.4 Participant numbering, treatment assignment, randomization

6.4.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant’s participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

A new ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed, and the participant will be assigned a new Participant No.

6.4.2 Treatment assignment, randomization

No randomization will be performed in this study. The assignment of a participant to a particular cohort will be coordinated by the sponsor.

6.4.2.1 Replacement policy

Participants may be replaced if they discontinue treatment early to ensure the required number of participants complete Part A for every cohort. Participants discontinuing treatment for safety reasons will not be replaced.

6.5 Treatment blinding

Not applicable, as this study is open-label without any randomization.

6.6 Dose escalation and dose modification

Investigational or other study treatment dose adjustments and/or interruptions are not permitted.

6.7 Additional treatment guidance

6.7.1 Treatment compliance

The investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the participant. This information should be captured in the source document at each visit. In addition, participants will be asked to complete a diary to record any missed doses. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

Off-site treatment administration compliance will be assessed by the off-site healthcare professional and information provided to the Investigator and/or study personnel.

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all participants treated with iptacopan as detailed in Section 8.5.2.

6.7.2 Recommended treatment of adverse events

The participants and treating staff need to be instructed to be vigilant for any clinical signs of bacterial infections (e.g., malaise, chills, fever, nausea, photophobia, generalized muscle and joint pain) and to measure the body temperature as per assessment schedule and at the times of symptoms of presumed infection. Participants will be instructed to contact the study physician immediately in case of suspicion of infection or elevated body temperature (> 38.3°C by oral or tympanic method) for a 'phone-directed' triage.

In case of a suspected bacterial infection, participants should be immediately considered for emergency evaluation and empirically treated with an appropriate antibiotic course.

In case of any (bacterial and non-bacterial incl. COVID-19) severe infection, interruption of iptacopan dosing should be considered, on a case-by-case basis. However, every effort should be taken to keep the participant on study treatment unless the risk outweighs the benefit in the opinion of the investigator.

Medication used to treat adverse events (AEs) must be recorded on the appropriate eCRF.

6.7.3 Emergency breaking of assigned treatment code

Not applicable.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH E6 GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational treatment can be found in the Investigator's Brochure (IB). This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Main study consent, which also included:
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
- As applicable, Pregnancy Outcomes Reporting Consent for female participants
- [redacted]
- As applicable, home nursing and/or participant transport consent (either as part of main consent or a dedicated consent)

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

[redacted]

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

The study includes the option for the participant to have certain study procedures performed off-site by an off-site healthcare professional instead of at the study site (not applicable for Cohort 2), for which a separate signature is required if the participant agrees. As applicable, this study includes optional support by a vendor to organize participants travel and accommodation if needed, for which a separate signature is required if the participant agrees. It is required as part of this protocol that the Investigator presents these options to the participant, as permitted by national and local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Health Authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1 and Table 8-3) lists all of the assessments and indicates when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the Assessment Schedule (Table 8-1 and Table 8-3) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Participants who discontinue study treatment should return for the end-of-treatment visit as soon as possible and attend the follow-up visits as outlined in the schedule.

Participants who discontinue from study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all of the assessments listed for the final visit (if treatment discontinuation EOT assessments, if FU discontinuation EOS assessments) will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications not previously reported must be recorded on the eCRF.

The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

When the following assessments are scheduled to be performed at the same time point, the following sequence is proposed:

1. [redacted]
2. ECGs
3. Vital signs
4. Blood sample collections
5. Drug administration

For PK profiling days, every effort should be made to take the PK sample at the protocol-specified time. Other assessments, e.g., [redacted] ECGs and vital signs, can be taken after the PK sample.

In case the investigator deems an unscheduled visit necessary, some or all of the following assessments may be conducted: Vital signs, physical exams, collection of safety lab and/or PK samples, and ECGs. Unscheduled PK samples should be taken as soon as possible but no later than 24 hours after the last dose of iptacopan.

Table 8-1 Assessment Schedule, Part A and washout

Period	Screening		Treatment Part A										Follow-up/Washout Part A				
Visit Name	Screening	Baseline	Treatment									EOT	Follow-up			EOS Part A	Post Study Safety Contact
Days Part A	-56 to -4	-7 to -2	1	8[2]	15		22[2]	29	43[2]	57[2]	71[2]	85	92[2,7]	99[7]	106[2,3,7]	113[4]	143
Weeks Part A	-8 to -1	-1	1	2	3		4	5	7	9	11	13	14	15	16	17	21
Time (post-dose)	-	-	-	-	0h	2h	-	-	-	0h	-	-	-	-	-	-	-
Informed consent	X																
[redacted]																	
Inclusion / Exclusion criteria	X	X															
Medical history/current medical conditions	X																
Prior medications	X																
Vaccination	X																
Demography	X																
Hepatitis and HIV Screen	S																
Body Height	X																
Body Weight	X		X		X			X		X		X				X	
Complete Physical Examination	S		S					S				S				S	
Body Temperature	X	X	X	X	X		X	X	X	X	X	X	X	X		X	
Blood Pressure	X	X	X		X	X		X				X				X	
Pulse rate	X	X	X		X	X		X				X				X	
Electrocardiogram (ECG)	X		X		X							X				X	
Pregnancy and assessments of fertility	S	S						S		S		S				S	
Hematology[1]	X	X	X	X[5]	X		X[5]	X	X[5]	X[5]	X[5]	X	X[5]	X	X[5]	X	
Clinical Chemistry	X				X			X				X				X	
Coagulation Panel	X				X			X				X				X	

Period	Screening		Treatment Part A										Follow-up/Washout Part A				
Visit Name	Screening	Baseline	Treatment									EOT	Follow-up			EOS Part A	Post Study Safety Contact
Days Part A	-56 to -4	-7 to -2	1	8[2]	15		22[2]	29	43[2]	57[2]	71[2]	85	92[2,7]	99[7]	106[2,3,7]	113[4]	143
Weeks Part A	-8 to -1	-1	1	2	3		4	5	7	9	11	13	14	15	16	17	21
Time (post-dose)	-	-	-	-	0h	2h	-	-	-	0h	-	-	-	-	-	-	-
Urinalysis	X				X			X				X				X	
Reproductive and thyroid hormones	X				X			X				X				X	
[redacted]																	
PK blood collection	See table below																
[redacted]																	
Patient diary			As required														
Study drug administration			Daily b.i.d.														
Concomitant medications	As required																
Adverse events/SAEs	As required																
Study completion information																X	
Safety Follow up Call																	S
Cohort 1 specific assessments																	
sC5b-9 for stratification	X	X															
[redacted]																	

Period	Screening		Treatment Part A									Follow-up/Washout Part A				
Visit Name	Screening	Baseline	Treatment								EOT	Follow-up			EOS Part A	Post Study Safety Contact
Days Part A	-56 to -4	-7 to -2	1	8[2]	15		22[2]	29	43[2]	57[2]	71[2]	85	92[2,7]	99[7]	106[2,3,7]	113[4]	143
Weeks Part A	-8 to -1	-1	1	2	3		4	5	7	9	11	13	14	15	16	17	21
Time (post-dose)	-	-	-	-	0h	2h	-	-	-	0h	-	-	-	-	-	-	-
[redacted]																	
Cohort 2 specific assessments																	
[redacted]																	

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Samples will be assessed at central lab for Cohort 1 (ITP) and locally for Cohort 2 (CAD)
[2] Visit may be performed at an off-site location as allowed by local laws and regulations (not applicable for Cohort 2).
[3] Visit only applicable to treatment responders.
[4] The Day 1 Part B visit is on the same day as EOS for Part A. Assessments listed in the Part A assessment schedule are applicable to all participants. Assessments listed in Part B assessment schedule are in addition and only applicable to responders continuing into Part B.
[5] No reticulocytes will be assess at this visit
[redacted]
[7] Responders reaching a critical cut-off level during washout (as defined in Section 3.1 in the cohort specific details) will have the opportunity to skip remaining follow-up visits and move to EOS Part A/Day 1 Part B visit before completion of the 4 weeks of washout.

Table 8-2 PK blood collection – Part A

Period	Visit Name	Days Part A	Weeks Part A	Time (post-dose)	PK blood collection
Treatment Part A	Treatment	1	1	-	
		8[1]	2	-	
		15	3	0h	X[2]
				0.5h	X
				1h	X
				2h	X
				4h	X
				6h	X
		22[1]	4	-	
		29	5	0h	X[2]
		43[1]	7	-	
		57[1]	9	0h	X[2]
				0.5h	X
				1h	X
				2h	X
				4h	X
				6h	X
		71[1]	11	-	
	EOT	85	13	-	

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[1] Visit may be performed at an off-site location as allowed by local laws and regulations.
[2] Directly before dosing

Table 8-3 Assessment Schedule, Part B

Period	Treatment Part B												Follow-up Part B			
Visit Name	Day 1 Part B	Treatment										EOT	Follow-up		EOS Part B	Post Study Safety Contact
Days Part B	1[2]	15	29	57[3]	85	169	253[3]	337	421[3]	505	617[3]	729	736[3]	743	757	787
Weeks Part B	1	3	5	9	13	25	37	49	61	73	89	105	106	107	109	113
Time (post-dose)	-	0h	-	0h	-	-	-	-	-	-	-	-	-	-	-	-
Body Weight				X		X		X		X		X			X	
Complete Physical Examination			S		S	S		S		S		S			S	
Body Temperature		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood Pressure			X		X	X		X		X		X			X	
Pulse rate			X		X	X		X		X		X			X	
Electrocardiogram (ECG)						X		X		X		X			X	
Hematology[5]		X	X[4]	X[4]	X	X	X[4]	X	X[4]	X	X[4]	X	X[4]	X	X	
Clinical Chemistry		X		X		X		X		X		X			X	
Coagulation Panel		X		X		X		X		X		X			X	
Urinalysis		X		X		X		X		X		X			X	
Reproductive and thyroid hormones		X		X		X		X		X		X			X	
PK blood collection		X[6]		X[6]												
Pregnancy and assessments of fertility			S	S	S	S	S	S	S	S	S	S			S	
[redacted]																
Patient diary	As required															
Study drug administration	Daily b.i.d.															
Concomitant medications	As required															
Adverse events/SAEs	As required															
Study completion information															X	
Safety Follow up Call																S
Cohort 1 specific assessments																
[redacted]																

Period	Treatment Part B												Follow-up Part B			
Visit Name	Day 1 Part B	Treatment										EOT	Follow-up		EOS Part B	Post Study Safety Contact
Days Part B	1[2]	15	29	57[3]	85	169	253[3]	337	421[3]	505	617[3]	729	736[3]	743	757	787
Weeks Part B	1	3	5	9	13	25	37	49	61	73	89	105	106	107	109	113
Time (post-dose)	-	0h	-	0h	-	-	-	-	-	-	-	-	-	-	-	-
[redacted]																
Cohort 2 specific assessments																
[redacted]																

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
[1] Measured at local labs (if available)
[2] The Day 1 Part B visit is on the same day as EOS for Part A. Assessments listed in the Part A assessment schedule are applicable to all participants. Assessments listed in Part B assessment schedule are in addition and only applicable to responders continuing into Part B.
[3] Visit may be performed at an off-site location as allowed by local laws and regulations (not applicable to Cohort 2).
[4] No reticulocytes will be assessed at this visit
[5] Samples will be assessed at central lab for Cohort 1 (ITP) and locally for Cohort 2 (CAD)
[6] Directly before dosing

8.1 Screening

Screening and re-screening

It is permissible to re-screen a participant if s/he fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

In the case where a safety laboratory assessment at screening and/or baseline is outside of the range specified in the eligibility criteria, the assessment may be repeated once prior to treatment assignment. If the repeat value remains outside of the specified ranges, the participant must be excluded from the study.

Use of medical history lab assessments

Medical history lab data can be taken into consideration for inclusion purposes when several repeat assessments are required to confirm eligibility (e.g., platelet count in Cohort 1 or hemoglobin level in Cohort 2). However, at least the baseline value must be from the study central laboratory (except for Cohort 2). If medical history lab data is used, values must be recorded in the eCRF.

If medical history data is not available, the screening period may consist of several visits for verification of these lab assessments.

Hepatitis screen, HIV screen

All participants will be screened for Hepatitis B surface antigen (HBsAg) and, if standard local practice, Hepatitis B core antigen (HBcAg). Screening for Hepatitis C will be based on HCV antibodies and, if positive, HCV RNA levels should be determined.

Table 8-4 Eligibility based on hepatitis B and C test results

	Scenario 1	Scenario 2	Scenario 3	Scenario 4
HBsAg/HBcAg	+	-	-	-
HCV Ab	Any	+	+	-
HCV RNA	Any	+	-	N/A
Eligibility	Not eligible	Not eligible	Eligible	Eligible

Evaluation for HIV seropositivity will be performed, and, if positive, confirmation by a second technique available at the laboratory site, e.g., Western blot. Appropriate counseling will be made available by the Investigator in the event of a positive confirmatory test. Notification of state and federal authorities, as required by law, will be the responsibility of the Investigator.

8.1.1 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be entered on the applicable eCRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event (SAE) during the screening period (see Section 10.1.3 for SAE reporting details).

Participants who sign an informed consent and are considered eligible but fail to be started on treatment for any reason will be considered early terminators. The reason for early termination should be captured on the appropriate disposition eCRF.

8.2 Participant demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with the eCRF.

Participant demographics: year of birth or age, sex, race/predominant ethnicity (if permitted) and relevant medical history/current medical conditions (until date of signature of informed consent) will be recorded in the eCRF. Where possible, the diagnosis and not symptoms should be recorded. Participant race/ethnicity data are collected and analyzed to identify any differences in the safety and/or efficacy profile of the treatment due to these characteristics. In addition, we need to assess the diversity of the study population as required by Health Authorities.

All prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start of the study must be documented. See the protocol Section 6.2.1 for further details on what information must be recorded on the appropriate page of the eCRF.

8.3 Efficacy

[redacted]

Cohort 1

The primary efficacy endpoint is based on platelet counts which will be measured as part of the hematology panel as described in Section 8.4.1.

Samples will be collected at the timepoints defined in the Assessment Schedule (Table 8-1 and Table 8-3). Follow instructions outlined in the Laboratory manual regarding sample collection, numbering, processing, and shipment.

Cohort 2

The primary efficacy endpoint is based on hemoglobin levels which will be measured as part of the hematology panel as described in Section 8.4.1.

Samples will be collected at the timepoints defined in the Assessment Schedule (Table 8-1 and Table 8-3). Follow instructions outlined in the Laboratory manual regarding sample collection, numbering, processing, and shipment.

8.3.1 Appropriateness of efficacy assessments

Cohort 1 - ITP

Efficacy assessments (platelet count) are standard, as done in daily clinical practice and driven by relevant guidelines: ASH 2019 guidelines for ITP (Neunert et al 2019) and updated international consensus report on the investigation and management of primary ITP (Provan et al 2019).

Cohort 2 - CAD

Efficacy assessments (hemoglobin level) are standard, as done in daily clinical practice and driven by relevant literature (Berentsen 2021).

8.4 Safety

Safety assessments are specified below with the Assessment Schedule (Table 8-1 and Table 8-3) detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE Section 10.1.

Table 8-5 Safety assessments

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A short physical exam will include the examination of general appearance. A short physical exam will be at all visits starting from Day 1 except where a complete physical examination is required (see above). Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs will include the collection of body temperature (recorded in °C), blood pressure and pulse measurements. The same route (temporal, tympanic, or axillary) and modality (temporal scanner, tympanic probe, thermometer) for body temperature monitoring should be used for ongoing participants to allow for accurate evaluation of the temperature trend. After the participant has been sitting for 3 minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured using an automated validated arm device, e.g., OMRON with an appropriately sized cuff. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. If vital signs are out-of-range two additional readings can be obtained, so that up to three consecutive assessments are made, with the participant

Assessment	Specification
	seated quietly for approximately five minutes preceding each repeat assessment. In case of repeated vital assessments, the eCRF should contain the last results.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured. Body mass index (BMI) will be calculated using the following formula: • BMI = Body weight (kg) / [Height (m)]^2

8.4.1 Laboratory evaluations

Safety laboratory evaluations are listed in Table 8-6 and the Assessment Schedule (Table 8-1 and Table 8-3) specifies when they should be performed.

Safety samples should be collected on site or off-site as specified in the Assessment Schedule. A central laboratory will be used for analysis of safety specimens collected as per assessment schedule. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the central laboratory manual.

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 [redacted]. 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.

Clinically notable laboratory findings are defined in Appendix 1 (Section 16.1). Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate.

In the case where a laboratory range is not specified by the protocol, but a value is outside the reference range for the laboratory at screening and/or initial baseline, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator (in consultation with the sponsor) and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once prior to treatment assignment.

All abnormal lab results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met. For those lab adverse events, repeated evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant.

In all cases, the Investigator must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the participant to continue in the study.

Table 8-6 Safety laboratory evaluations

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Ery. Mean Corpuscular Hemoglobin, Ery. Mean Corpuscular HGB Concentration, Ery. Mean Corpuscular Volume, Platelets, Erythrocytes, Leukocytes, Erythrocyte Cell Morphology (if available at local lab and indicated based on flagged blood count results), Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands), Reticulocytes (selected visits as per assessment schedule)
Chemistry	Albumin, Alkaline phosphatase (ALP), ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphate, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, Triglycerides, Ferritin, Urea Nitrogen or Urea, Uric Acid, Amylase, Lipase, Glucose, Haptogloblin (Cohort 2 CAD only), estimated GFR
Urinalysis[1]	Dipstick measurements for protein, bilirubin, blood, glucose, ketones, nitrites, pH, specific gravity and urobilinogen, and WBC/leukocytes will be performed at the site's local laboratory. If dipstick measurement results are positive (abnormal), results will be captured in the eCRF. Microscopy must be assessed locally following an abnormal dipstick test.
Coagulation	Prothrombin time (PT), International normalized ratio (INR), Activated partial thromboplastin time (APTT)
Thyroid	Triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone (TSH) and reverse T3
Reproductive hormones	Testosterone, Dihydrotestosterone (DHT), Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH)
Hepatitis markers	Hepatitis B Virus Surface Antigen (HBsAg), Hepatitis C Virus (HCV) antibodies; If HCV antibodies is positive, HCV RNA will be analyzed
HIV	HIV seropositivity testing will be performed as detailed in the Central laboratory manual and in line with local regulatory requirements
Hepatic follow-up	These tests are in addition to routine testing, to be performed only in follow-up to safety events as indicated in Appendix 2 (Section 16.2), hepatic event follow-up
Pregnancy Test	Serum / Urine pregnancy test (see Section 8.4.3)

[1]A midstream urine sample (approx. 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments.

8.4.2 Electrocardiogram (ECG)

Electrocardiograms (ECGs) must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The Fridericia QT correction formula (QTcF) must be used for clinical decisions. The investigator must calculate QTcF if it is not auto-calculated by the ECG machine.

ECGs will be locally collected and evaluated. Interpretation of the tracing must be made by a qualified physician and documented on the appropriate eCRF. Each ECG tracing should be labeled with the study number, participant initials (where regulations permit), participant number, date, and kept in the source documents at the study site. Clinically significant abnormalities present at screening should be reported on the appropriate eCRF. Clinically

significant findings must be discussed with Novartis prior to enrolling the participant in the study. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

The original ECGs on non-heat-sensitive paper or a certified copy on non-heat sensitive paper, appropriately signed, must be archived at the study site.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. For any ECGs with participant safety concerns (please refer to Appendix 1 (Section 16.1) for notable abnormalities), two additional ECGs must be performed to confirm the safety finding. Single 12 lead ECGs are to be recorded approximately 2 minutes apart. ECG safety monitoring, or a review process, should be in place for clinically significant ECG findings at baseline before administration of study treatment and during the study.

Clinically significant abnormalities must be recorded on the eCRF as either medical history/current medical conditions or adverse events as appropriate.

8.4.3 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing as per the Assessment Schedule (see Table 8-1 and Table 8-3). At screening and baseline serum pregnancy tests are required. At further visits urine test will be done. A positive urine test needs to be confirmed by a serum test. Additional pregnancy testing might be performed if requested by local requirements. Additional local requirements would be specified in the local ICF.

If participants cannot visit the site to have serum pregnancy tests during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the Site is informed and can verify the pregnancy test results (e.g., following country specific measures).

Assessments of fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female participant regardless of reported reproductive/menopausal status at screening/baseline.

8.4.4 Appropriateness of safety measurements

The safety assessments selected are standard for the indications/participant populations.

8.5 Additional assessments

[redacted]

[redacted]

Patient Diary

Patient diaries will be used to record any missed administration of iptacopan.

8.5.2 Pharmacokinetics

PK samples will be collected at the visits defined in the Assessment Schedule (Table 8-1 and Table 8-3). Instructions regarding sample collection, numbering, processing and shipment are outlined in the laboratory manual. See Section 8.5.3.2 for the potential use of residual samples. At the Day 15 and Day 57 visits, a PK profile will be collected up to 6 hours post dose. At other specified visits, trough levels will be collected by sampling just before receiving the morning or evening dose.

Plasma samples for analysis of PK parameters will be obtained and evaluated in all participants receiving iptacopan. No whole blood or urine samples will be collected for PK analysis. [redacted]

Iptacopan will be determined by a validated LC-MS/MS method with a previously established Lower Limit of Quantification (LLOQ) of 1 ng/mL. Iptacopan plasma concentration will be expressed in mass per volume units (ng/mL) and refer to the free base. Due to the limited sampling interval of 6 hours, the calculated PK parameters will be limited to the following, determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 8 or higher): Cmax, Tmax, AUClast and AUCtau. The latter will be calculated by the "last observation carried forward" approach, assuming that, at steady-state, trough levels at T=0hr are the same as for T=12hr (tau). The approach will be applied as sampling times are limited to 6 hours and the extrapolation of AUClast (0-6hrs) to AUCtau (0-12hrs) is likely to exceed the accepted value of 20% of the total AUC. The linear trapezoidal rule will be used for AUC calculation.

Concentrations below the LLOQ will be reported as zero and missing data will be labeled as such in the Bioanalytical data report (BDR).

[redacted]

[redacted]

[redacted]

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study drug administration, if any) and can be initiated by either the participant or the investigator.

The investigator must discontinue study treatment for a given participant if he/she believes that continuation would negatively impact the participant's well-being.

Discontinuation from study treatment is required under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment Section 6.2.2
- Any situation in which continued study participation might result in a safety risk to the participant
- If a liver event occurs, follow the Hepatotoxicity Clinical Safety Standard Guideline, outlined in Appendix 2 (Section 16.2) regarding discontinuation of study treatment.
- Increases in QTcF to >500 ms or of >60 ms over baseline
- Unsatisfactory therapeutic effect (decision to be taken after consultation with Sponsor).

If discontinuation from study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant’s discontinuation from study treatment and record this information.

Participants who discontinue from study treatment are to return for the end of treatment and follow-up visits indicated in the Assessment Schedule (refer to Section 8).

After discontinuation from study treatment, participants (responders, in particular) should be closely monitored for a drop in their peripheral blood counts and associated signs and symptoms, in line with their underlying disease (e.g., platelet count for ITP, hemoglobin level for CAD). Any rescue therapy should be initiated as clinically indicated.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

At a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 8).

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent/oppose to the use of their data/biological samples, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.2 Withdrawal of informed consent/Opposition to use data/biological samples

Withdrawal of consent/opposition to use data/biological samples occurs when a participant:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples)

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be in writing (depending on local regulations) and recorded in the source documentation.

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/opposition to use data/biological samples and record this information.

Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the participant therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their Personal Data.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table (refer to Section 8).

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

9.3 Study stopping rules

The Sponsor will review emergent safety data on an ongoing basis to react as soon as there is a possibility that a stopping rule could apply. The Sponsor will review all SAEs as individual cases and review summaries of non-serious AEs for patterns and trends, after excluding any events clearly not related to iptacopan treatment (e.g., SAE that occurred during the pre-treatment screening period, or disease-related SAE expected in the population under study).

The following stopping rules apply separately to each cohort. Enrollment in the affected cohort and dosing of affected participant(s) with iptacopan will be paused if any of the following occurs during the study:

- Two or more SAEs within the same cohort considered by the Investigator to be potentially related to iptacopan OR
- One life-threatening or fatal SAE considered by the Investigator to be potentially related to iptacopan

The cohort may resume following a full safety review if both the Investigator and Sponsor agree it is safe to proceed. Dependent on regional guidances, any restart following a temporary hold due to stopping rules being met will require prior submission and approval of a substantial CTA amendment to the competent authorities.

9.4 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their Study Completion visit (either EOS for Part A or Part B) 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. Each participant will be required to complete the study in its entirety.

Once planned enrollment numbers are met, participants who already signed the consent but not yet treated will be allowed to continue into the study.

All treated participants should have a safety follow-up call conducted 30 days after last visit. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the participant should be recorded in the source documentation.

Please see Section 6.1.4 for post trial access.

Continuing care should be provided by the investigator and/or referring physician after the EOS visit as per local standard of care.

9.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination may include:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment: Participants who discontinue from study treatment are to return for the end of treatment and follow-up visits indicated in the Assessment Schedule (Section 8). The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

10 Safety monitoring, reporting and committees

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade:
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates or ongoing) and the outcome must be reported
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased

- Drug interrupted/permanently discontinued

6. Its outcome

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Appendix 1 (Section 16.1).

10.1.1.1 Adverse events of special interest

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, data from preclinical studies and include infections caused by encapsulated bacteria.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal

- life-threatening: life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the participant's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred (see Section 10.1.5).

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days after the last study visit must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded on the electronic Serious Adverse Event (eSAE)

Report Form with paper backup; all applicable sections of the form must be completed in order to provide a clinically thorough report.

SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety (CMO & PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period after the last study visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

10.1.4 Pregnancy reporting

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

Post-natal follow up should occur at 1, 3 and 12 months after delivery.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Table 16-1 in Appendix 2 (Section 16.2) for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-1
Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate eCRF.

Following should be considered when managing the participant:

- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
    - Obtaining more detailed history of symptoms and prior or concurrent diseases
    - Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
    - Exclusion of underlying liver disease

The investigator can include based on investigator's discretion:

- Imaging such as abdominal US, CT or MRI, as appropriate
- Considering gastroenterology or hepatology consultations.

All follow-up information and procedures performed must be recorded as appropriate in the eCRF.

10.3 Committees

Not applicable.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded/entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis or delegated CRO representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the

study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

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 sC5b-9 stratification group (sC5b-9 high, sC5b-9 low).

12.1 Analysis sets

For all analysis sets, participants will be analyzed according to the study treatment(s) received.

The safety analysis set will include all participants who received any study drug.

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 with relevant impact on PK data.

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

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by cohort and group for the full analysis set.

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 summarized by system organ class and preferred term, by cohort and group.

12.3 Treatments

The Safety set will be used for the analyses below.

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

The duration of exposure in days/weeks to iptacopan will be summarized by means of descriptive statistics using the safety set.

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

12.4 Analysis supporting primary objectives

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.

12.4.1 Definition of primary endpoint(s)

The primary 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.

Please refer to Section 2.1 for a description of the primary estimand.

12.4.2 Statistical model, hypothesis, and method of analysis

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

Cohort 1

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

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.

12.4.3 Handling of intercurrent events of primary estimand

The intercurrent events of the primary estimands are part of the primary variable, defined in Section 2.1.

12.4.4 Handling of missing values not related to intercurrent event

Missing data imputations will be discussed in the Statistical Analysis Plan (SAP) in detail.

12.4.5 Sensitivity analyses

Not applicable

12.4.6 Supplementary analysis

Not applicable

12.5 Analysis supporting secondary objectives

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

In this section, all the measurements collected will be summarized descriptively by cohort and group and listed.

12.5.1.1 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.

Summary statistics will be provided for the time to first response by cohort and group. In addition, time to first response will be presented graphically for all the participants by cohort and group. Additional analysis will be detailed in the SAP.

12.5.1.2 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.

Summary statistics will be provided for duration of response by cohort and group. In additional, duration of response will be presented graphically for all the participants by cohort and group.

12.5.1.3 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 points.

Summary statistics for change from baseline will be presented by cohort, group and visit and time point. The magnitude of response will be categorized by cohort and group. The response categories will be provided in SAP.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by cohort (for ITP, both groups (sC5b-9 high and sC5b-9 low) will be pooled).

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

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 any study treatment.

Adverse events

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 and preferred term.
- by primary system organ class, preferred term and maximum severity.

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.

The number (and proportion) of participants with adverse events of special interest/related to identified and potential risks will be summarized by cohort and group.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

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.

Vital signs

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 will be provided by cohort, group and visit/time.

Clinical laboratory evaluations

All laboratory data parameters will be listed by cohort, group, participant, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by cohort, group and visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

12-lead ECG

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 analysis of QT/QTcF interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT/QTcF intervals or changes from baseline will be presented. 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.

12.5.2.1 The need for rescue therapy during Part A

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

12.5.3 Pharmacokinetics

Descriptive summary statistics of iptacopan plasma concentration data will be provided by treatment, and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Descriptive summary statistics for PK parameters will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is *Tmax* where median, minimum, and maximum will be presented.

Table 12-1 Non-compartmental pharmacokinetic parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1)
AUCinf	The AUC from time zero to infinity (mass x time x volume-1)
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1)
Cmax	The maximum (peak) concentration observed in plasma, after oral administration (mass x volume-1) of iptacopan
Tmax	The time to reach maximum (peak) plasma concentration after oral administration (time) of iptacopan
Lambda_z	Smallest (slowest) disposition (hybrid) rate constant (time-1) may also be used for terminal elimination rate constant (time-1)
T1/2	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives

12.5.4 Biomarkers

The effect of iptacopan on relevant disease biomarkers not covered in the primary objective during Part A will be assessed. The biomarkers includes lactate dehydrogenase (LDH), total bilirubin, reticulocyte count and haptoglobin.

Descriptive statistics and change from baseline will be summarized by cohort and group.

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12.7 Interim analyses

The following interim analyses 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/or 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 might be conducted during the study 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.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

12.8.1.1 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.

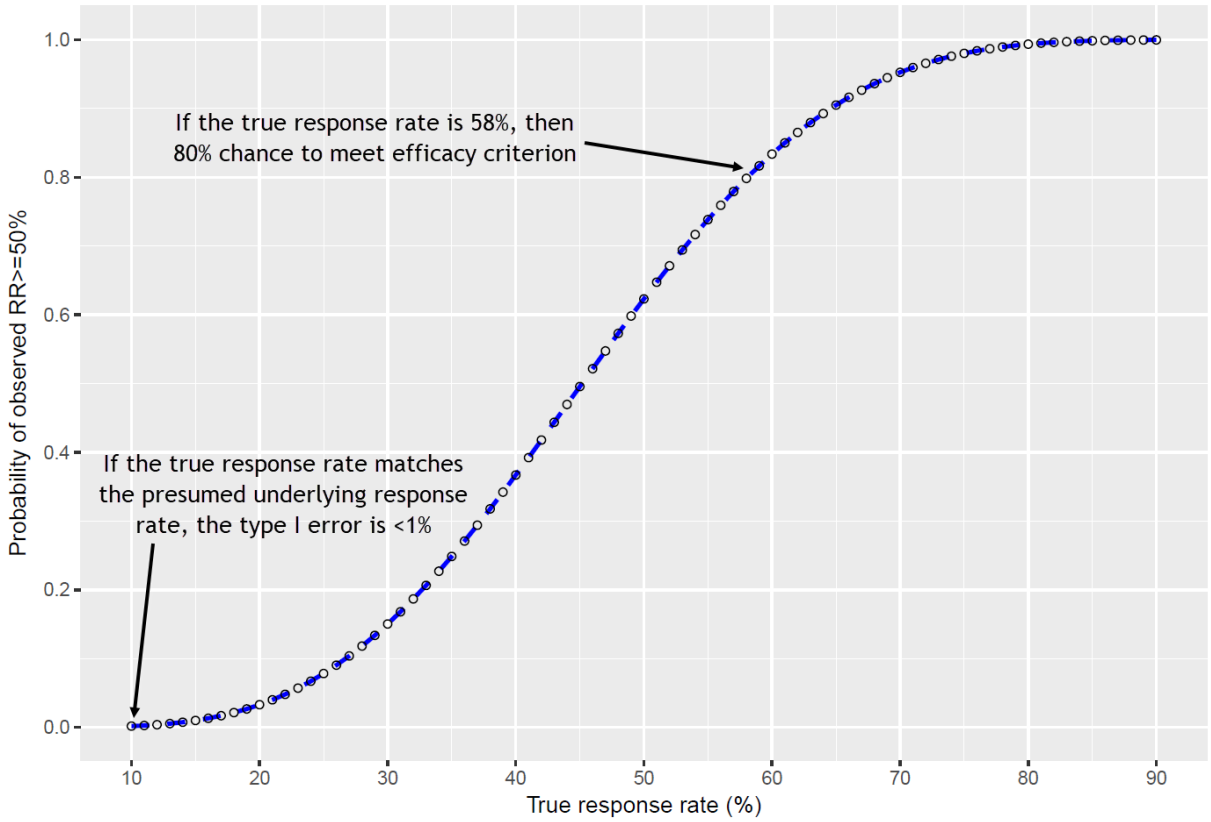
Complement-activated group (N=10):

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 12-1 Probability of observed response rate of ≥50 percent vs. true response rate



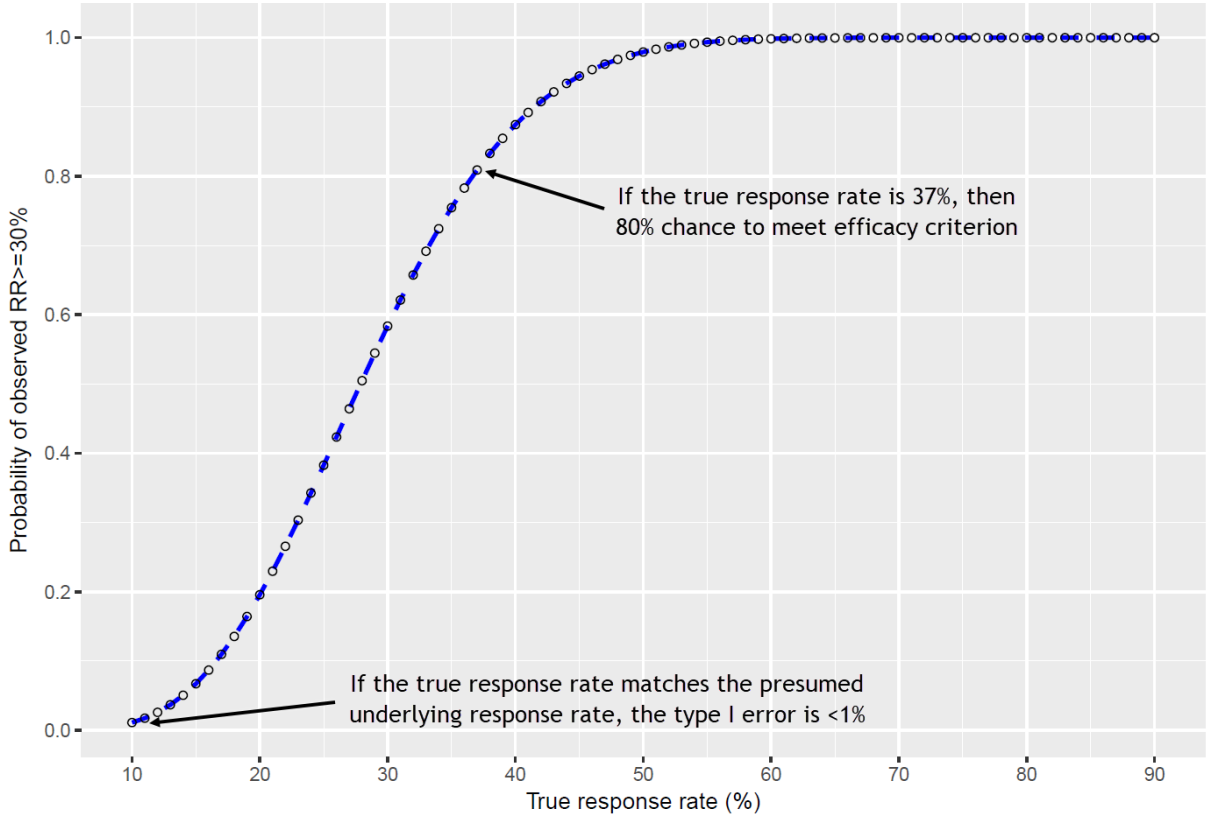
All-comers (N=20):

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 12-2 Probability of observed response rate of ≥30 percent vs. true response rate



12.8.1.2 Cohort 2: CAD (N=10)

The proposed sample size for CAD cohort is 10 and hence the sample size calculations are the same as for the ITP complement-activated group (see Section 12.8.1.1).

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement

to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last participant last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

13.5 Participant Engagement

The following participant engagement initiatives are included in this study and will be provided, as available and approved locally, for distribution to study participants at the timepoints indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Thank You letter
- Plain language trial summary - after CSR publication
- Individual treatment information - after database lock

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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[redacted]

16 Appendices

16.1 Appendix 1: Clinically notable laboratory values

Renal alert values

Once a participant is exposed to study treatment, the following two categories of abnormal renal laboratory alert values should be assessed during the study period:

- 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.

ECG alert values

- Resting heart rate sinus rhythm < 30 or a HR decrease ≥ 25% or
- HR > 130 [bpm]
- QRS >120 or increase >25% compared to predose baseline [msec]
- QTcF >500 or increase >60 compared to predose baseline [msec]*
- Ventricular tachycardia
- New complete heart block (Grade III AV block) or Mobitz II AV block

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

*Please check Section 9.1.1 for study treatment discontinuation.

16.2 Appendix 2: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-1 Definitions of Triggers, Actions and Follow-up requirements for liver events

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case (Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN – or 3 x ULN in the presence of bone pathology)	· Discontinue the study treatment immediately (if possibly related to study treatment) · Hospitalize, if clinically appropriate · Establish causality (investigate alternative etiologies)[a] · Record the AE and contributing factors (e.g. concomitant medication, medical history, laboratory value) in the appropriate eCRF	· ALT, AST, TBL, Alb, PT/INR, ALP, GGT, CK and GLDH (frequency at Investigator discretion) · Monitor for symptoms[b] · Report outcome[c]
ALT		
> 8 × ULN	· Interrupt the study treatment (if possibly related to study treatment) · Hospitalize if clinically appropriate · Establish causality (investigate alternative etiologies)[a] · Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	· ALT, AST, TBL, Alb, PT/INR, ALP and GGT (frequency at Investigator discretion) · Monitor for symptoms[b] · Report outcome[c]
> 3 × ULN and INR > 1.5 (in the absence of anticoagulation) If elevated at baseline: > 2 x baseline or > 300 U/L (whichever occurs first)	· Interrupt the study treatment (if possibly related to study treatment) · Hospitalize if clinically appropriate · Establish causality (investigate alternative etiologies)[a] ● Study drug can be restarted only if alternative etiology is identified and liver enzymes return to baseline · Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	· ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion)
> 5 to ≤ 8 × ULN If elevated at baseline: > 3 x baseline or > 300 U/L (whichever occurs first)	· Repeat LFT within 48 hours · If elevation persists, continue follow-up monitoring · If elevation persists for more than 2 weeks, discontinue the study drug · Establish causality (investigate alternative etiologies)[a] · Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	· ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion)

Criteria	Actions required	Follow-up monitoring
> 3 × ULN to ≤ 5 × ULN (accompanied by symptoms)[b] If elevated at baseline: > 2 x baseline or > 300 U/L (whichever occurs first)	· Interrupt the study treatment (if possibly related to study treatment) · Hospitalize if clinically appropriate · Establish causality (investigate alternative etiologies)[a] ● Study drug can be restarted only if alternative etiology is identified and liver enzymes return to baseline · Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	· ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion) · Monitor for symptoms[b] · Report outcome[c]
> 3 to ≤ 5 × ULN (participant is asymptomatic)[b] If elevated at baseline: > 2 x baseline or > 300 U/L (whichever occurs first)	· Repeat LFT within the next week · If elevation is confirmed, initiate close observation of the participant	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology) >3 x ULN in the presence of bone pathology	· Repeat LFT within 48 hours · If elevation persists, establish causality (investigate alternative etiologies)[a] · Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Liver events		
Jaundice	· Interrupt the study treatment (if possibly related to study treatment) · Hospitalize if clinically appropriate · Establish causality (investigate alternative etiologies)[a] ● Study drug can be restarted only if alternative etiology is identified and liver enzymes return to baseline · Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	· ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion) · Monitor symptoms[b] · Report outcome[c]

Criteria	Actions required	Follow-up monitoring
Any AE potentially indicative of a liver toxicity[d]	· Consider study treatment interruption or discontinuation · Hospitalization if clinically appropriate · Establish causality (investigate alternative etiologies)[a] · Record the AE and contributing factors (e.g. con meds, med hx, lab) in the appropriate eCRF	Investigator discretion

[a] Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

[b]Severe fatigue, malaise (general), abdominal pain (right upper quadrant), nausea, vomiting or rash with eosinophilia

[c]Resolved = return to Day 1 values; Condition unchanged = stable values at three subsequent monitoring visits at least 2 weeks apart; Condition deteriorated = values worsen or liver transplantation; and Fatal.

[d]These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms.

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