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Novartis Research and Development

MBG453/Sabatolimab

Clinical Trial Protocol CMBG453B12203 / NCT04812548

A single-arm, open-label, Phase II study of sabatolimab in combination with azacitidine and venetoclax in adult participants with high or very high risk myelodysplastic syndrome (MDS) as per IPSS-R criteria

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Table of contents

[redacted]

[redacted]

[redacted]

List of tables

[redacted]

List of figures

[redacted]

List of abbreviations

ADA	Anti-drug antibody
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
APTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
AUC	Area under the curve
BCL-2	B-cell lymphoma 2
BCRP	Breast cancer resistance protein
BMA	Bone marrow aspirate
BMI	Body Mass Index
BSA	Body surface area
BUN	Blood Urea Nitrogen
CABG	Coronary artery bypass graft
CDP	Clinical Development Plan
CK	Creatinine Kinase
CMML	Chronic myelomonocytic leukemia
CO	Country Organization
COA	Clinical Outcome Assessment
COVID-19	Coronavirus disease 2019
CR	Complete remission
CRF	Case Report/Record Form (paper or electronic)
CRi	Complete Remission with incomplete hematologic recovery
CRO	Contract Research Organization
CSR	Clinical study report
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	Cytochrome P450
DBP	Diastolic Blood Pressure
DDI	Drug-drug interaction
DDS	Dose Determining Set
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
ECOG	Eastern Cooperative Oncology Group

[redacted]

EDC	Electronic Data Capture
EFS	Event-free survival
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
ELN	European Leukemia Network
EMA	European Medicines Agency
EOT	End of treatment
ePRO	Electronic Patient Reported Outcome
[redacted]	[redacted]
ESA	Erythropoiesis Stimulating Agent
eSAE	Electronic Serious Adverse Event
ESMO	European Society for Medical Oncology
eSource	Electronic Source
EWOC	Escalation with overdose control
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy- Fatigue
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
G-CSF	Granulocyte-colony stimulating factor
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GLDH	Glutamate dehydrogenase
h	Hour
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C Virus
HEOR	Health Economics & Outcomes Research
HI	Hematological improvement
HIV	Human immunodeficiency virus
HMA	Hypomethylating agents
HSCT	Hematopoietic Stem Cell Transplant
i.v.	intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive care unit
IEC	Independent Ethics Committee
IG	Immunogenicity

[redacted]

INR	International Normalized Ratio
IPSS-R	Revised International Prognostic Scoring System
irAE	Immune related adverse event
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
IWG	International Working Group
LC-MS	Liquid chromatography-mass spectrometry
LDH	lactate dehydrogenase
LFS	Leukemia-free survival
LFT	Liver function test
LUC	Large unstained cells
mCR	Marrow complete remission
MDRD	Modification of Diet in Renal Disease
MDS	Myelodysplastic syndromes
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MPN	Myeloproliferative neoplasm
MRD	Measurable residual disease
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
[redacted]	[redacted]
NK	Natural killer
NTproBNP	N-terminal prohormone of brain natriuretic peptide
ORR	Overall response rate
OS	Overall survival
PAS	Pharmacokinetic Analysis Set
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Progressive Disease
PD-1	Programmed cell death protein 1
PFS	Progression-free survival
[redacted]	[redacted]
[redacted]	[redacted]
Pgp	P-glycoprotein
PK	Pharmacokinetic(s)
PR	Partial Remission
PRO	Patient Reported Outcomes
Q4W	every 4 weeks
QTcF	QT interval corrected by Fridericia's formula

[redacted]

[redacted]	[redacted]
RBC	red blood cell(s)
RNA	Ribonucleic acid
RoW	Rest of World
[redacted]	[redacted]
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome Coronavirus 2
SBP	Systolic Blood Pressure
SCT	Stem cell transplant
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SJS	Steven-Johnson syndrome
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total bilirubin
TEN	Toxic epidermal necrolysis
TIM-3	T-cell immunoglobulin domain and mucin domain-3
TLS	Tumor lysis syndrome
TSH	Thyroid-Stimulating Hormone
ULN	upper limit of normal
ULQ	upper limit of quantification
USPI	United States Prescribing Information
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of study Consent

[redacted]

Glossary of terms

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
Cohort	A specific group of participants fulfilling certain criteria and generally treated at the same 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
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
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
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
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	An individual who has consented to participate in this study. The term participant may be used to describe either 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.
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.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study

[redacted]

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
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
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 completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
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
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
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.
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)	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

Amendment 2 (06-Oct-2021)

Amendment rationale

As of the release of this amendment, 9 sites have been initiated, 9 participants have been screened and 5 participants have received study treatment in this trial.

The purpose of the amendment is to clarify DLT criteria (Table 6-4) to specify that prolonged cytopenias beyond Day 42 from the start of a study treatment cycle should be considered DLTs and to clarify language around intercurrent events in the estimand section as well as analysis of duration of response.

Additionally, language around COVID-19 vaccines and time frame for SAE follow-up reporting was added.

Changes to the protocol

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

- Section 6.2.2: wording around COVID-19 vaccination added
- Section 6.5.1.3 and section 12.1: Number of venetoclax doses for a participant to be evaluable for DLT updated to match the venetoclax regimen
- Section 6.5.2: Update definition of hematological toxicity DLT criteria to clarify persistent grade 4 cytopenias beyond Day 42 from the start of a study treatment cycle should be considered DLTs
- Section 6.5.2: Update to DLT criteria with respect to blood bilirubin increased
- Section 6.5.2: Adding a formal DLT criteria for grade 4 non-hematologic toxicity
- Section 6.5.2: Clarify that Grade 3 nausea, vomiting or diarrhea not requiring tube feeding, total parenteral nutrition, or prolonged hospitalization are exceptions to DLT criteria
- Section 9.1.1.2: remove start of a new antineoplastic treatment (including HSCT) as a reason for discontinuing post-treatment follow-up
- Section 10.1.3: Clarify that 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, and under no circumstances later than within 24 hours of the investigator receiving the follow-up information
- Section 12.4.1.2: Clarify that CR achieved after initiation of a new antineoplastic therapy will not be considered for the primary endpoint
- Section 12.5.1.1: Clarify that Transfusion dependence is defined as a minimum 3 units of transfusion received within the 8 consecutive weeks prior to start of treatment
- Section 12.5.1.2: Clarify that duration of CR, duration of CR/mCR, duration of response will be derived regardless of HSCT and to perform two supplementary analyses

[redacted]

- Section 12.5.1.2: Clarify that PFS, EFS, LFS events will be counted regardless of HSCT but censored in case of events after initiation of a new antineoplastic therapy
- Section 2 (Table 2-1); Section 4.4.1; Section 8.3.1 (Table 8-2) Definition of CR/mCR was updated to match the definition of CR in table 8-2

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.

[redacted]

Amendment 1 (17-May-2021)

Amendment rationale

As of the release of this amendment, no site has been initiated, no participant has been screened and no participant has received study treatment in this trial.

The purpose of the amendment is to address Health Authorities' requests (from Belgium and France) to specify that women of childbearing potential using a hormonal contraception should add a barrier method, as stated in the venetoclax SmPC, and to add a cross-reference to venetoclax local label in the prohibited medication section (Section 6.2.2).

Additionally, preliminary results of the first cohort of the safety run-in of CMBG453C12201 study are included. The pharmaceutical dose form and route of administration terms for azacitidine have been updated to be in alignment with other sabatolimab protocols. Lastly, one clarification to the analysis of primary endpoints is added.

Changes to the protocol

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

- Section 4.2: Update the clinical safety data with the preliminary results from the first five patients treated with the triplet sabatolimab-venetoclax-azacitidine combination on the CMBG453C12201 study.
- Section 5.2: Amend exclusion criterion 17 to specify that women of childbearing potential using a hormonal contraception should add a barrier method as stated in the venetoclax SmPC.
- Section 6.1.1: Update the dosage form and route of administration of azacitidine to align with other sabatolimab study protocols.
- Section 6.2.2: Clarify that prohibited medication related to both azacitidine and venetoclax will apply according to local label.
- Section 12.4.1: Clarify further the efficacy analysis: to count CR after progression and to censor time to event endpoints in case of a new antineoplastic therapy.

In addition, format and grammatical updates are made throughout the protocol to improve flow and consistency.

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 Form. Sites are required to update and submit for approval a revised Informed Consent Form taking into account the changes described in this protocol amendment.

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Protocol summary

Protocol number	CMBG453B12203
Full Title	A single-arm, open-label, phase II study of sabatolimab in combination with azacitidine and venetoclax in adult participants with high or very high risk myelodysplastic syndromes (MDS) as per IPSS-R criteria
Brief title	A study of sabatolimab in combination with azacitidine and venetoclax in high or very high risk MDS participants
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Biological
Study type	Interventional
Purpose and rationale	Sabatolimab, a novel monoclonal antibody inhibitor of TIM-3, has shown preliminary evidence of clinical activity as a single-agent in participants with MDS. The study will be conducted in two parts. The primary purpose of Part 1 (Safety run-in) is to rule out excessive toxicity of sabatolimab, when administered in combination with azacitidine and venetoclax. The primary purpose of the combined cohort 2 of the Safety run-in (Part 1) and Expansion (Part 2) is to evaluate efficacy of sabatolimab, when administered in combination with azacitidine and venetoclax in adult participants with high or very high risk MDS. The current trial will seek to extend the preliminary findings of efficacy of sabatolimab in combination with hypomethylating agents (HMA) by evaluating sabatolimab in combination with the HMA azacitidine and the Bcl-2 inhibitor venetoclax in adult participants with higher-risk MDS (per IPSS-R). The doublet of venetoclax and azacitidine has demonstrated improved efficacy relative to azacitidine alone in early phase Ib trials (DiNardo et al 2019), and recently has received regular approval by the FDA (on 16-Oct-2020) for treatment of newly diagnosed AML, or who have comorbidities precluding intensive induction chemotherapy. More recently, a Phase Ib trial conducted in higher-risk MDS participants indicated that the combination of venetoclax and azacitidine is feasible and reported also promising preliminary results in this patient population. The recommended schedule for further development of venetoclax in combination with azacitidine in MDS will be used in this trial (Wei et al 2019).
Primary Objective(s)	**Safety run-in (Part 1):**

	To determine whether sabatolimab is safe when added to azacitidine + venetoclax in participants with high or very high risk MDS as per IPSS-R criteria **Cohort 2 of the Safety run-in (Part 1) and Expansion (Part 2):** To determine the complete remission (CR) rate of sabatolimab (800 mg Q4W) in combination with azacitidine and venetoclax.
Secondary Objectives	**Safety run-in (Part 1) and Expansion (Part 2):** • To assess Complete Remission (CR) + marrow complete remission (mCR) rate • To assess Overall Response Rate (ORR) defined as [CR + mCR + partial remission (PR) + HI] • To assess the improvement of RBC/platelets transfusion independence • To assess the safety and tolerability of sabatolimab in combination with azacitidine and venetoclax • To further characterize the pharmacokinetics of sabatolimab • To characterize the immunogenicity of sabatolimab in combination with azacitidine and venetoclax **Cohort 2 of the Safety run-in (Part 1) and Expansion (Part 2):** • To assess Duration of CR • To assess Duration of CR/mCR • To assess Duration of response • To assess Time to CR/mCR • To assess Progression Free Survival (PFS) • To assess Leukemia-Free survival (LFS) • To assess Event-Free Survival (EFS) • To assess Overall Survival **Expansion (Part 2):** • To evaluate changes from baseline in fatigue
Study design	This phase II, open-label, single-arm, multi-center study of sabatolimab in combination with azacitidine and venetoclax in adult participants with high or very high risk MDS as per IPSS-R criteria will be conducted in two parts. Part 1 is a Safety run-in part of approximately 18 participants, to assess whether sabatolimab at the two dose levels tested consecutively (400 mg Q4W: cohort 1 of Safety run-in and then 800 mg Q4W: cohort 2 of Safety run-in) is safe when given in combination with fixed dose of azacitidine and venetoclax in MDS patients. Following the

	observation period, a Safety Review Meeting will be conducted for each dose level. If no safety concerns are identified with the tested combination of sabatolimab at 400 mg Q4W, azacitidine and venetoclax, then the second dose level (800 mg Q4W) will open to enrollment. Thereafter, if no safety concerns are identified with the tested combination of sabatolimab at 800 mg Q4W, azacitidine and venetoclax, Novartis will provide notification to the investigational sites that Part 2 of study testing this dose level in a larger group of participants (Expansion) is open to enrollment. Otherwise the study will be stopped. Part 2 is an Expansion part to further assess efficacy and safety of sabatolimab at 800 mg Q4W in combination with venetoclax and azacitidine. Enrollment to Expansion (Part 2) will continue until enrollment of approximately 58 additional participants has been achieved. The total sample size (Part 1 and Part 2) of the study is approximately 76 participants i.e. approximately 6 participants in cohort 1 of Part 1 testing sabatolimab at 400 mg Q4W, 12 participants in cohort 2 of Part 1 testing sabatolimab at 800 mg Q4W and 58 participants in Expansion (Part 2) further testing sabatolimab at 800 mg Q4W.
Study population	The study population will include approximately 76 adult participants with high or very high risk MDS, as per the revised International Prognostic Scoring System (IPSS-R).
Key Inclusion criteria	1. Signed informed consent must be obtained prior to participation in the study 2. Age ≥ 18 years at the date of signing the informed consent form (ICF) 3. Morphologically confirmed diagnosis of myelodysplastic syndrome (MDS) based on 2016 WHO classification (Arber et al, 2016) by local investigator assessment with one of the following Prognostic Risk Categories, based on the revised International Prognostic Scoring System (IPSS-R) (Greenberg et al 2012): • Very high (> 6 points) • High (> 4.5-6 points) 4. Not immediately eligible for hematopoietic stem-cell transplantation (HSCT) or intensive chemotherapy at the time of screening due to individual clinical factors such as age, comorbidities and performance status, donor availability (de Witte et al 2017) 5. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2

Key Exclusion criteria	1. Prior exposure to TIM-3 directed therapy or any BCL-2 inhibitor (including venetoclax) at any time 2. Prior therapy with immune check point inhibitors (e.g. anti-CTLA4, anti-PD-1, anti-PD-L1, or anti-PD-L2) or cancer vaccines is not allowed if the last dose of the drug was administered within 4 months prior to start of treatment 3. Previous first-line treatment for very high risk or high risk myelodysplastic syndromes (based on IPSS-R, Greenberg et al 2012 and Arber et al, 2016) with any antineoplastic agents, approved or investigational, including for example chemotherapy, lenalidomide and hypomethylating agents (HMAs) such as decitabine or azacitidine However, a one single cycle of HMAs treatment only started prior to enrollment is allowed. 4. Live vaccine administered within 30 days prior to start of treatment 5. Current use or use within 14 days prior to start of treatment of systemic steroid therapy (> 10 mg/day prednisone or equivalent) or any immunosuppressive therapy. Topical, inhaled, nasal, ophthalmic steroids are allowed. Replacement therapy, steroids given in the context of a transfusion, are allowed and not considered a form of systemic treatment 6. History of severe hypersensitivity reactions to any ingredient of study drug(s) (azacitidine, venetoclax or sabatolimab) or monoclonal antibodies (mAbs) and/or their excipients 7. Participants with Myelodysplastic syndrome (MDS) based on 2016 WHO classification (Arber et al, 2016) with revised International Prognostic Scoring System (IPSS-R) ≤ 4.5
Study treatment	Sabatolimab + azacitidine + venetoclax
Efficacy assessments	Disease response will be assessed locally by the investigator in all participants (MDS) according to modified IWG criteria for MDS and WHO criteria (Cheson et al 2000, Cheson et al 2006, Arber et al, 2016, Platzbecker 2019). Bone marrow aspirate (BMA)/biopsy and peripheral blood will be collected at screening and at regular intervals during treatment and efficacy follow-up phase for assessment of disease. Participants can be assessed for disease response at any time if clinically indicated, for example in case of suspicion of progression/relapse.
Pharmacokinetic assessments	Pharmacokinetic (PK) samples will be obtained and evaluated in all participants.

Key safety assessments	· Adverse event monitoring, · Physical examination, · Vital signs, · ECOG PS, · Monitoring of laboratory evaluations in blood and urine, · 12-lead electrocardiograms (ECGs).
Other assessments	**Clinical Outcomes Assessment:** [redacted] In addition, [redacted], the Functional Assessment of Chronic Illness Therapy Fatigue scale (FACIT-Fatigue) [redacted] [redacted] [redacted] **Immunogenicity:** Immunogenicity samples will be obtained and evaluated in all participants.
Data analysis	For participants included in the Safety run-in (Part 1), the tolerability of the two tested dose levels of sabatolimab (two consecutive cohorts at 400 mg Q4W (with approximately 6 participants) and then 800 mg Q4W (with approximately 12 participants) administered in

[redacted]

	combination with venetoclax and azacitidine will be guided by a Bayesian analysis based on the DLT incidence reported during the two first cycles as well as an overall safety overview. The probability that the true DLT rate is ≥ 33% (i.e. overdose criteria) will be modeled using a Bayesian Model. If the dose of 400 mg Q4W (cohort 1) meets overdose criteria with at least 3 evaluable participants, the study will be stopped. If the dose of 400 mg Q4W does not meet overdose criteria, cohort 2 with sabatolimab 800 mg Q4W will be opened with approximately 12 participants. If the dose of 800 mg Q4W meets overdose criteria with at least 9 evaluable participants, Part 2 (Expansion) will not be opened and the study will be stopped. Otherwise, Part 2 (Expansion) will be opened at 800 mg Q4W of sabatolimab (see Figure 3-1). For all participants treated with sabatolimab at 800 mg Q4W, the efficacy of sabatolimab in combination with venetoclax and azacitidine will be based on the proportion of participants achieving a complete remission (CR) as per investigator assessment. Trial success will be assessed based on dual decision criterion with a null value (no effect) of 39% (statistical criteria) and a minimum estimated effect size (clinical relevance) of 50% (clinical criteria) for the CR rate. If the statistical and clinical criteria are both met, the trial will be declared successful. With two criteria stated above, approximately 70 participants (including participants from cohort 2 of the Safety run-in (Part 1) and Expansion part) are required. Therefore, the total sample size is 76 participants (including the 6 participants treated at 400 mg Q4W in the Cohort 1 of the Safety run-in (Part 1)). AL least thirty six participants with CR out of 70 are needed to declare the trial successful. For a true CR rate of 55.7% (i.e. 39 participants with CR), the probability for the trial success is 80% (power).
Key words	Phase II, sabatolimab, TIM-3, venetoclax, azacitidine, Myelodysplastic syndromes (MDS).

1 Introduction

1.1 Background

It is estimated that 15,000 to 20,000 new cases of Myelodysplastic Syndromes (MDS) are diagnosed annually in the USA (Klepin 2016). In Europe, the incidence rate of MDS is about 2 new cases per 100,000 each year (Visser et al 2012). The incidence of MDS is more frequent in male patients and increases with age, with a median age at diagnosis of about 70 years.

MDS correspond to a heterogeneous group of hematological malignancies that are associated with impaired bone marrow function, ineffective hematopoiesis, elevated bone marrow blasts and persistent peripheral blood cytopenias. Cytogenetics abnormalities are frequently present at time of diagnosis. Patients with MDS have a predisposition to developing acute myeloid leukemia (AML) (Heaney and Golde 1999). Although progression to AML can frequently lead to death in patients with MDS, many deaths are consequences of cytopenias and marrow failure in the absence of leukemic transformation. To account for disease heterogeneity, assess the risk of progression to AML and estimate survival, MDS prognostication systems have been proposed. In the context of a clinical trial, prognosis is usually determined using the revised International Prognostic Scoring System (IPSS-R), which considers the percentage of bone marrow blasts, the number of cytopenias, and bone marrow cytogenetics. Patients with untreated MDS are stratified into five IPSS-R prognostic risk categories: very low, low, intermediate, high and very high. In a large database of MDS patients (n = 7,012), distribution of patients across the 5 IPSS-R risk categories were as follows: very low (19%), low (38%), intermediate (20%), high (13%) and very high (10%) (Greenberg et al 2012). For high and very high risk MDS patients, the prognosis is dismal: median survival times are limited (1.6 years and 0.8 years, respectively) and risk of leukemic transformation is high (time to observe 25% AML transformation rate in this group of patients is 1.4 and 0.73 years, respectively). Current treatment guidelines for patients with high and very high risk MDS recommend hematopoietic stem cell transplantation (HSCT) in rare patients who are eligible for this procedure , intensive chemotherapy or hypomethylating agents (HMAs; azacitidine and decitabine) (Fenaux et al 2014; Platzbecker 2019). Choice of therapy is mainly driven by the IPSS-R score, the overall general health status and clinical assessment of comorbidities, and donor availability for a transplant. For patients eligible for HSCT or for whom the marrow blast count requires reduction, intensive chemotherapy may be considered and may precede HSCT (Steensma 2018). HSCT remains the only curative option for MDS patients; however, many MDS patients are not candidates for HSCT (Passweg et al 2011; de Witte et al 2017). In MDS patients who are classified as high, very high risk by IPSS-R, and who do not qualify for HSCT or intensive chemotherapy, HMAs are the first-line reference treatment. Azacitidine is the sole HMA which demonstrated a prolongation of overall survival (OS) compared to conventional care regimens among patients with higher-risk MDS [median OS, 24.5 versus 15 months, respectively, hazard ratio (HR) = 0.58; P < 0.0001] in the pivotal AZA-001 randomized phase III trial (Fenaux et al 2009). Other controlled clinical trials reported lower median OS between 19 to 20 months in patients receiving azacitidine (Silverman et al 2002). Azacitidine is generally administered for a minimum of 6 cycles (repeat cycle after 4 weeks), and continued for as long as the patient benefits.

[redacted]

In clinical practice, azacitidine safety profile is mainly characterized by bone marrow suppression leading to dose-reduction or temporary or permanent discontinuations of azacitidine. Supportive care, including blood transfusions, is frequently required during the course of the disease. HMAs have improved outcomes for patients with high risk/very high risk MDS; especially for patients who are not candidates for intensive chemotherapy regiments or HSCT. However, despite these improvements, prognosis for patients treated with HMAs remains poor. Median survival in high and very high MDS patients are only 1.6 years and < 1 year respectively (Greenberg et al 2012). Treatment failure, relapse and transformation to acute myeloid leukemia (AML) are frequent events. Once a patient with higher risk MDS has failed treatment with HMAs or transformation to AML has occurred, survival generally will not exceed 6 months. Thus, improved treatments in addition to HMAs and/or as an alternative to HMAs are urgently warranted in this MDS patient population.

Novel targeted therapies and immune checkpoint inhibitors are being clinically studied in MDS such as venetoclax and immunotherapeutic agents.

In 2018, venetoclax, a small molecule inhibitor of BCL-2, the over-expression of which has been implicated in the maintenance and survival of AML cells and has been associated with resistance to chemotherapeutics (Kojima et al 2006), has received full approval by the FDA (on 16-Oct-2020) in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed AML in adults who are age 75 years or older, or who are unfit for intensive induction chemotherapy. Approval was based on two open-label, non-randomized trials, and efficacy was established based on the rate of complete remission (CR) and CR duration. In a most recent data update (DiNardo et al 2019), it is reported that the CR and CRi rates were 37% and 30% respectively, for patients treated with venetoclax in combination with azacitidine or decitabine, with a median observed time in remission (CR or CRi) of 11.3 months (95% CI, 8.9 months-not reached). Furthermore, only 29% of patients in remission achieved levels of MRD below 0.1%, suggesting that deep leukemic clearance (< 0.1%) remains a challenge for a majority of the patients. Thus, although these results represent an advance in treatment of the unfit AML population, remission duration and leukemic clearance to MRD levels below 0.1% is still modest, and an unmet need remains for new therapy options for this patient population.

More recently, a Phase Ib trial conducted in higher-risk MDS participants indicated that the combination of venetoclax and azacitidine is feasible and reported promising preliminary results (Wei et al 2019). In this trial, the Complete Remission (CR) rate per IWG - MDS criteria was approximately 38%, median time to CR about 2 months and the 12-month estimate duration of CR was about 83%.

The safety profile of the combination is reported to be manageable and mainly consists of myelosuppression including neutropenia, febrile neutropenia, thrombopenia and anemia. The recommended dose for Phase II trial of venetoclax is 400 mg for days 1-14 of a 28-day cycle when combined with azacitidine (75mg/m^2, days 1-7). Recent retrospective studies of real world experience (Ball et al 2020, Azizi et al 2020) evaluating venetoclax in association with HMA to treat higher-risk MDS participants confirmed the feasibility of this regimen, overall good tolerability and reported promising signs of efficacy with overall hematological response rates reaching approximately 75% in HMA-naive participants. Consistent with the findings of aforementioned Phase Ib trial (Wei et al 2019), these studies recommended the use of an

abbreviated dosing schedule for venetoclax (i.e. 400 mg for days 1 to 14 of a 28-day cycle) in order to manage optimally the myelosuppression.

Blocking Programmed cell death protein 1/ligand (PD-1/PD-L1) or Cytotoxic T Lymphocyte Associated Protein 4 (CTLA4) pathways enhances anti-leukemia responses by unleashing T-cells in murine models of AML/MDS. In addition, there is evidence of pharmacodynamic activity and promise for checkpoint inhibition in MDS (Chen et al 2008, Zhang et al 2009, Yang et al 2014, Kong et al 2015, Ørskov et al 2015); however, it will be important to determine the ideal checkpoint inhibitor strategy and to consider combination therapies in order to optimize anti-tumor immunity. A few clinical trials have investigated immune checkpoint inhibitors in MDS and AML participants. An ongoing Phase II study investigates the clinical effects of the checkpoint inhibitors nivolumab (PD1) and ipilimumab (CTLA4) with or without the hypomethylating agent azacitidine in front-line and relapsed MDS participants. Front-line MDS participants were treated with the combination azacitidine+nivolumab or ipilimumab, whereas relapsed MDS participants received single-agent nivolumab or ipilimumab. Twenty participants were treated with azacitidine+nivolumab, 21 with azacitidine+ipilimumab, 15 with nivolumab, and 20 with ipilimumab. The observed overall response rate was 75%(15/20), 71% (15/21), 13% (2/15), and 35% (7/20) of participants treated with azacitidine combined with nivolumab, azacitidine combined with ipilimumab, nivolumab, and ipilimumab, respectively; Complete Remission or Complete Remission with residual thrombocytopenia was observed in 10/20 (50%), 8/21 (38%), 0 (0%), and 3 (15%) in participants treated with azacitidine combined with nivolumab, azacitidine combined with ipilimumab, nivolumab, and ipilimumab, respectively. Main toxicities reported were as follows: skin rash (11%); fatigue (9%); pain (7%); infection (6%); febrile neutropenia (5%); pruritus (6%); diarrhea (5%); constipation, nausea (4% each), alanine aminotransferase (ALT) elevations, anorexia, cough (3% each). This provides preliminary evidence that checkpoint inhibition combined with hypomethylating agents is feasible in front-line MDS and may have clinical activity (Daver et al 2019). A Phase Ib/II study involving azacitidine and nivolumab has been conducted in 70 relapsed/refractory AML participants. The overall response rate (ORR) in this study was 33%: 23 clinical responses were reported including 4 complete remission, 11 complete remission with insufficient recovery of counts (CRi), 1 partial remission (PR), and 7 participants with hematologic improvement (HI) maintained > 6 months. The ORR was 58% and 22% in HMA-naive (n = 25) and HMA pre-treated (n = 45) participants, respectively. Duration of response among responders was 5.2 months. Three participants in CR/CRi underwent HSCT. Additionally, 6 participants had stable disease lasting for more than 6 months.

Overall the combination azacitidine plus nivolumab was well tolerated. Grade 3 or 4 immune related adverse events (irAE) occurred in 8 (11%) participants (Daver et al 2019). A Phase Ib study reported that ipilimumab in participants with MDS after HMA failure is safe but has limited efficacy as monotherapy. However, prolonged stable disease was reported and some participants received allo HSCT. Prolonged stable disease for ≥ 46 weeks occurred in 7 participants (24% of the participants), including 3 participants with more than a year of stable disease. 5 participants underwent allografting without excessive toxicity (Zeidan et al 2018).

T-cell immunoglobulin domain and mucin domain- 3 (TIM-3; also known as hepatitis A virus cellular receptor 2) is a negative regulator of T-cells (immune checkpoint). TIM-3+

hematopoietic stem cells from participants with MDS display aberrant differentiation, increased proliferation and decreased apoptosis (Sakuishi et al 2011). TIM-3 is overexpressed in bone marrow mononuclear cells and detection on blasts increases as MDS progresses. Therefore the blockade of this immune checkpoint constitutes a potential target for novel therapies in MDS, and promising preclinical and clinical anti-cancer activity has been reported for TIM-3 blockade (Kikushige et al 2010, Sakuishi et al 2010, Ngiow et al 2011, Sakuishi et al 2011, Jing et al 2015, Asayama et al 2017). Sabatolimab (MBG453) is a high-affinity, ligand-blocking, humanized anti TIM-3 IgG4 antibody which blocks the binding of TIM-3 to phosphatidylserine (PtdSer). First in human trials have shown that sabatolimab can be safely administered including with decitabine or azacitidine in MDS/AML participants. Preliminary clinical activity has been observed particularly in high and very high risk MDS participants (see clinical responses in Section 4.3).

There are ongoing Phase II trial [CMBG453B12201] and Phase III trial [CMBG453B12301] which are investigating sabatolimab in higher risk MDS participants. These trials are double-blind placebo-controlled studies comparing sabatolimab plus HMA versus placebo plus HMA. Another ongoing single-arm, open label, Phase II trial [CMBG453C12201] is investigating sabatolimab in combination with venetoclax and azacitidine in AML participants.

For further details about sabatolimab, refer to the IB [MBG453 Investigator's Brochure].

1.2 Purpose

The current study will enroll untreated adult participants with high or very-high risk MDS (per IPSS-R criteria) and it will be conducted in two sequential parts (see Figure 3-1).

The primary purpose of the Safety run-in (Part 1) is to rule out excessive toxicity and investigate safety of 400 mg (Cohort 1 of Part 1) first and then 800 mg (Cohort 2 of Part 1) sabatolimab when administered every 4 weeks in combination with azacitidine and venetoclax. Cohort 2 will be opened only if data from Cohort 1 does not indicate excessive toxicity of the sabatolimab 400 mg Q4W dose level. Thereafter, Expansion (Part 2) will be opened only if data from Cohort 2 does not indicate excessive toxicity of the sabatolimab 800 mg Q4W dose level. If overdose criteria are met in Cohort 2, then the study will be stopped (See Figure 3-1).

The primary purpose of the Expansion (Part 2) is to enroll additional participants in order to evaluate further efficacy, safety, tolerability and characterize the pharmacokinetics of sabatolimab at 800 mg Q4W when administered in combination with azacitidine and venetoclax. The complete remission rate will be determined in all participants (i.e. enrolled in Cohort 2 of Part 1 and Expansion) treated with sabatolimab at 800 mg Q4W with azacitidine and venetoclax.

Sabatolimab is a novel monoclonal antibody inhibitor of TIM-3. In study [CPDR001X2105], sabatolimab was safe and well tolerated and has shown promising evidence of efficacy, including durable CRs, when administered in combination with HMA (decitabine or azacitidine) in newly diagnosed higher-risk MDS participants. The current trial will seek to extend these preliminary findings of efficacy by evaluating sabatolimab in combination with azacitidine and venetoclax. The doublet of venetoclax and azacitidine has demonstrated improved efficacy relative to azacitidine alone in AML patients (DiNardo et al 2019). Recently, venetoclax has received approval by FDA for treatment of unfit AML patients on 16-Oct-2020. Several prospective and retrospective trials (Ball et al 2020, Wei et al 2019, Azizi et al 2020,

[redacted]

reported also promising efficacy and acceptable safety profile of the doublet of venetoclax and azacitidine in participants with higher-risk MDS. Despite the improved efficacy suggested by the addition of venetoclax to azacitidine in higher-risk MDS, a significant unmet medical need remains as a substantial number of participants still do not achieve durable CR (complete response).

2 Objectives and endpoints

The objectives and associated endpoints are presented in Table 2-1 below:

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• **Safety run-in (Cohort 1 and Cohort 2 of Part 1)** To determine whether sabatolimab is safe when added to azacitidine + venetoclax in participants with high or very high risk MDS per IPSS-R criteria	• Incidence of DLTs between Cycle 1 Day 8 and end of Cycle 2
• **Cohort 2 of Safety run-in (Part 1) and Expansion (Part 2)** To determine the complete remission (CR) rate of sabatolimab in combination with azacitidine and venetoclax in participants with high or very high risk MDS as per IPSS-R criteria treated with sabatolimab at 800 mg Q4W.	• Proportion of participants from cohort 2 of Part 1 and Part 2 achieving CR according to investigator assessment (per modified IWG-MDS - Cheson 2006 criteria). CR is defined as follow: bone marrow blasts <=5%, hemoglobin level ≥ 10 g/dL, platelets count ≥ 100*10^9/L, neutrophils count ≥ 1.0*10^9/L, absence of blasts in peripheral blood (Please see Section 12.4 for estimand definition).
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• **Safety run-in (Part 1) and Expansion (Part 2)**	
• To assess the [CR + marrow complete remission (mCR)] rate	• Proportion of participants with [CR + marrow complete remission (mCR)] according to investigator assessment by dose level for the safety run-in part (cohort 1 (400 mg Q4W) and cohort 2 (800 mg Q4W)) and for participants treated with sabatolimab 800 mg (Q4W) (cohort 2 of safety run-in and expansion parts).
• To assess Overall Response Rate (ORR), per modified IWG-MDS Cheson 2006 criteria, defined as the proportion of participants achieving [CR + mCR + partial remission (PR) + hematologic improvement (HI)]	• Overall Response Rate (ORR) is the proportion of participants who achieved HI or better as best response as per investigator assessment (per modified IWG-MDS Cheson 2006 criteria). ORR will be summarized by dose level for the safety run-in part (cohort 1 (400 mg Q4W) and cohort 2 (800 mg Q4W)) and for participants treated with sabatolimab 800 mg (Q4W) (cohort 2 of safety run-in and expansion parts).

Objective(s)	Endpoint(s)
• To assess the improvement in RBC/platelets transfusion independence	• Proportion of participants who are RBC/platelets transfusion independent and duration of transfusion independence (Section 8.3) as per IWG-MDS by dose level for the safety run-in part (cohort 1 (400 mg Q4W) and cohort 2 (800 mg Q4W)) and for participants treated with sabatolimab 800 mg (Q4W) (cohort 2 of safety run-in and expansion parts).
• To characterize the safety profile of sabatolimab when administered in combination with azacitidine and venetoclax	• Incidence and severity of AEs and SAEs, changes in laboratory values and vital signs, and incidence of notable ECG abnormalities by dose level for the safety run-in part (cohort 1 (400 mg Q4W) and cohort 2 (800 mg Q4W)) and for participants treated with sabatolimab 800 mg (Q4W) (cohort 2 of safety run-in and expansion parts).
• To further characterize the pharmacokinetics of sabatolimab when administered in combination with azacitidine and venetoclax	• Serum concentrations and pharmacokinetic parameters (see Section 8.5.2) for sabatolimab by dose level for the safety run-in part (cohort 1 (400 mg Q4W) and cohort 2 (800 mg Q4W)) and for participants treated with sabatolimab 800 mg (Q4W) (cohort 2 of safety run-in and expansion parts).
• To characterize the immunogenicity of sabatolimab when given in combination with venetoclax and azacitidine	• Anti-drug Antibody (ADA) prevalence at baseline and ADA incidence on-treatment by dose level for the safety run-in part (cohort 1 (400 mg Q4W) and cohort 2 (800 mg Q4W)) and for participants treated with sabatolimab 800 mg (Q4W) (cohort 2 of safety run-in and expansion parts).
• **Cohort 2 of Safety run-in (Part 1) and Expansion (Part 2)**	
• To assess duration of CR	• Duration of CR is defined as time from first occurrence of CR to relapse from CR, progression or death due to any cause whichever occurs first for participants treated with sabatolimab at 800 mg Q4W.
• To assess time to CR/mCR	• Time to CR/mCR is defined as time from start of treatment to first occurrence of CR or mCR as per investigator assessment for participants treated with sabatolimab at 800 mg Q4W.
• To assess duration of CR/mCR	• Duration of CR/mCR is defined as time from first occurrence of CR/mCR to relapse from CR, progression or death due to any cause whichever occurs first for participants treated with sabatolimab at 800 mg Q4W.
• To assess duration of response (responding participants defined as hematological improvement (HI) or better, per modified IWG-MDS	• Duration of response for participants who achieved HI or better per modified IWG-MDS Cheson 2006 criteria) as per investigator assessment until relapse or death. Participants who did not relapse or die are censored to last adequate response assessment

[redacted]

Objective(s)	Endpoint(s)
Cheson 2006 criteria) as per investigator assessment.	for participants treated with sabatolimab at 800 mg Q4W.
• To assess Progression-Free Survival (PFS)	• Time from start of treatment to disease progression (including transformation to acute leukemia per WHO 2016 classification), relapse from CR or death due to any cause, whichever occurs first for participants treated with sabatolimab at 800 mg Q4W.
• To assess Leukemia-Free Survival (LFS)	• Time from start of treatment to transformation to acute leukemia [as defined as ≥ 20% blasts in bone marrow/ peripheral blood (per WHO 2016 classification) or diagnosis of extramedullary acute leukemia or death due to any cause, whichever occurs first] for participants treated with sabatolimab at 800 mg Q4W.
• To assess Event-free Survival (EFS)	• Time from start of treatment to lack of reaching CR within the first 6 cycles, relapse from CR or death due to any cause, whichever occurs first for participants treated with sabatolimab at 800 mg Q4W.
• To assess Overall Survival (OS)	• Time from start of treatment to death due to any cause for participants treated with sabatolimab at 800 mg Q4W.
• **Expansion (Part 2)**	
• To evaluate the changes from baseline in fatigue	• Changes in fatigue as measured by the FACIT-Fatigue for participants treated with sabatolimab at 800 mg Q4W of the expansion part only.

[redacted]

Objective(s)	Endpoint(s)
[redacted]	

3 Study design

This Phase II, open-label, single-arm, multi-center study of sabatolimab in combination with azacitidine and venetoclax in adult participants with high or very high risk MDS as per IPSS-R criteria is described in Figure 3-1 below. The study will enroll a total of approximately 76 participants and will be conducted in two sequential parts:

- **Part 1:** Safety run-in consists of 2 subsequent cohorts of 400 mg Q4W (cohort 1) and 800 mg Q4W (cohort 2) of sabatolimab in combination with fixed dose of venetoclax and azacitidine. Cohort 2 will be open only after the review of safety data from cohort 1 indicates the regimen is safe. If the regimen using sabatolimab at 400 mg Q4W is not safe, the study will be stopped. Subsequently, if the review of safety data from participants enrolled in cohort 2 indicates that the regimen is safe, then Part 2 will be opened. Otherwise, if the regimen at 800 mg Q4W is not safe, the study will be also stopped.

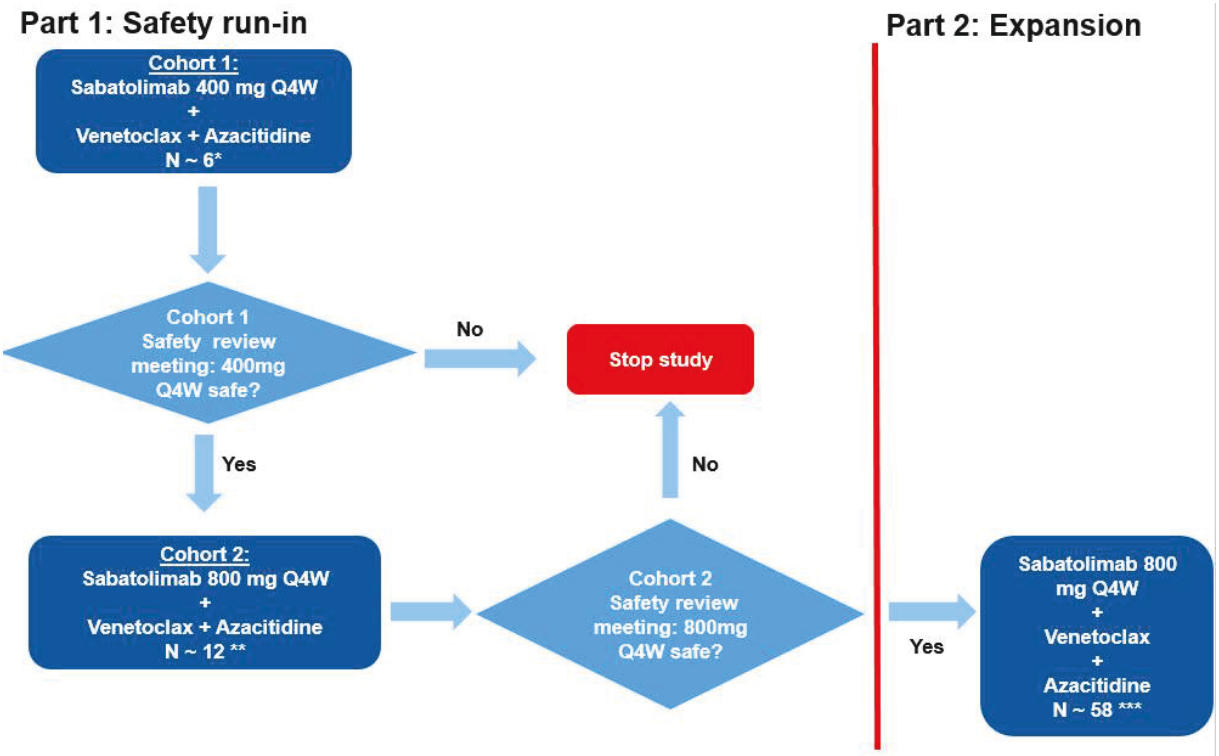
[redacted]

- **Part 2:** Expansion will enroll additional participants to further investigate the regimen including sabatolimab at 800 mg Q4W, azacitidine and venetoclax. Participants data from Part 1 and Part 2 treated with 800 mg Q4W will be combined to determine the complete remission rate.

Part 1 is a Safety run-in to assess whether sabatolimab (400 mg Q4W and subsequently 800 mg Q4W) is safe when given in combination with fixed dose of azacitidine and venetoclax. A total of approximately 18 participants will be enrolled to Part 1 across the two dose levels. Approximately 6 participants will be initially enrolled at the starting dose level, 400 mg Q4W (cohort 1), in order to obtain at least 3 evaluable participants (see Section 6.5.1.3 for evaluability criteria). If the dose level of sabatolimab 400 mg Q4W in combination with azacitidine and venetoclax is assessed to be safe, then a second cohort of participants investigating sabatolimab at 800 mg Q4W combined to azacitidine and venetoclax (cohort 2) will be opened. Otherwise, the study will be stopped. Approximately 12 participants will be enrolled in cohort 2, in order to obtain at least 9 evaluable participants (see Section 6.5 for evaluability criteria). If the combination regimen used in cohort 2 is safe then the Expansion part will be opened (Part 2). Otherwise the study will be stopped. For each dose level, once the required number of evaluable participants has been confirmed, enrollment will be halted until participants have completed the DLT observation period (see Section 6.5), and a Safety Review Meeting has been conducted (see Section 6.5.1). If no safety concerns are identified at either dose level (see Section 12.4.2 for statistical model, hypothesis, and method of analysis as well as Section 6.5.1.3 for guidelines to assess tolerability), Novartis will provide notification to the investigational sites that Expansion (Part 2) of the study is open to enrollment. Enrollment to Part 2 will continue until a total enrollment of approximately 70 participants treated at the sabatolimab dose of 800 mg Q4W (including the participants treated in cohort 2 in the Safety run-in (Part 1) and participants treated in the Expansion (Part 2)) has been achieved.

[redacted]

Figure 3-1 Study design



* The Safety run-in cohort 1 investigating sabatolimab 400 mg Q4W requires at least 3 evaluable participants (6 enrolled participants) to have been observed for at least 2 cycles.
** The Safety run-in cohort 2 investigating sabatolimab 800 mg Q4W requires at least 9 evaluable participants (12 enrolled participants) to have been observed for at least 2 cycles.
*** To achieve 70 participants at the dose level 800 mg Q4W

Hospitalization is required at Cycle 1 from Day 1 to Day 3 for participants participating to Safety run-in (cohorts 1 and 2) in order to monitor closely the chemistry parameters, in particular to detect occurrence of TLS, (see Section 6.5.4.2), and thereafter at the discretion of the investigator. Study treatment will be administered in cycles with a planned duration of 28 days, and study treatment may continue until the participant experiences disease progression (Fenaux et al 2014) or unacceptable toxicity.

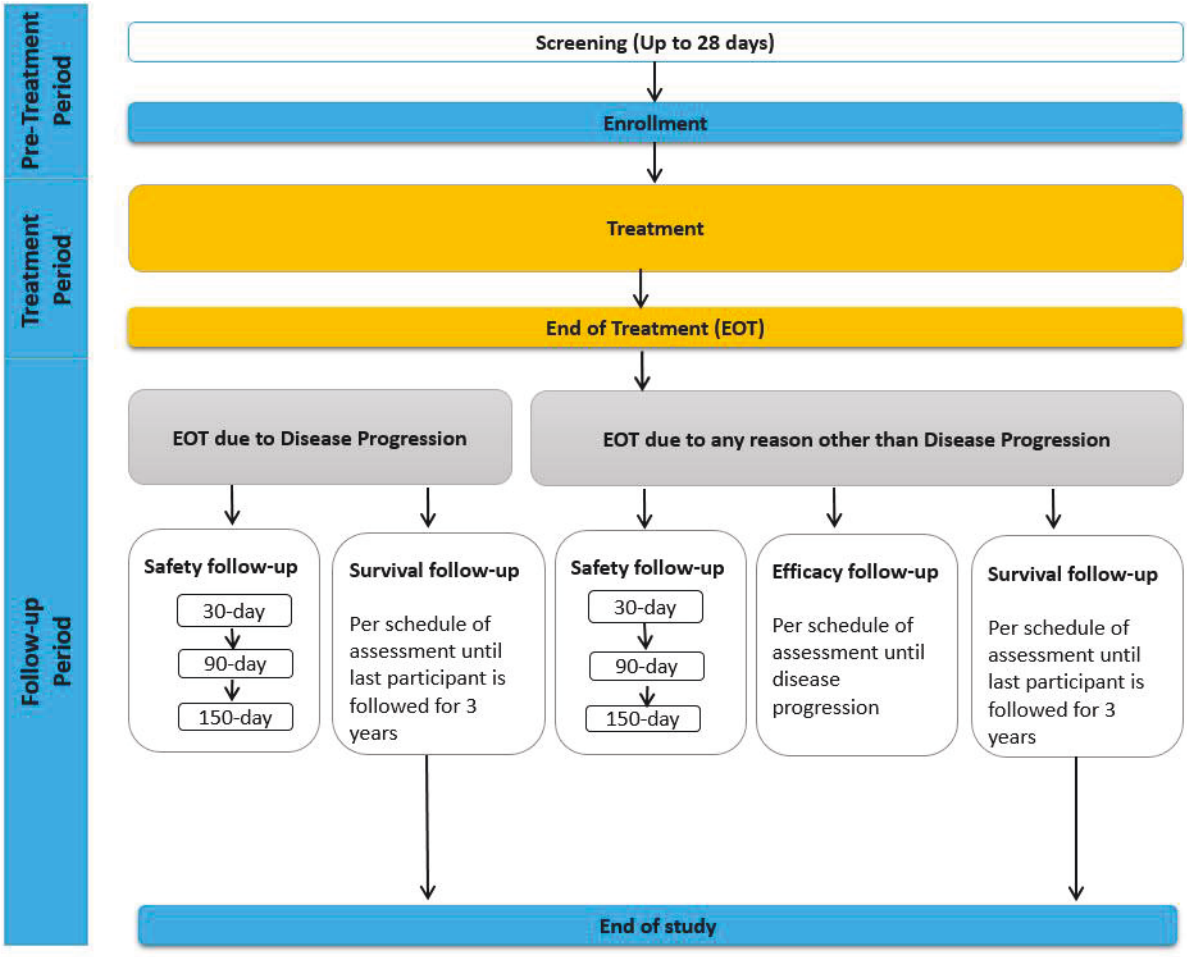
In each 28 day-cycle:

- azacitidine will be administered intravenously or subcutaneously at 75 mg/m^2 on Days 1 to 7 (or, at discretion of the investigator on Days 1-5 and Day 8-9), during Safety run-in (Part 1) and Expansion (Part 2).
- venetoclax will be administered orally at 400 mg daily for 14 consecutive days, during Safety run-in (Part 1) and Expansion (Part 2). No ramp-up of venetoclax is necessary in this trial (see Section 4.3).
- sabatolimab will be administered intravenously at 400 mg (during Safety run-in cohort 1) or 800 mg (during Safety run-in cohort 2 and Expansion) on Day 8 (Q4W).

At any time during the study, participants unable to tolerate one or two of the study treatment drugs, may continue study treatment with only the tolerated drug(s). Use of prophylactic antibiotics as per institutional guidelines is mandatory at Cycle 1; and thereafter prophylactic antibiotics may be used at the physician's discretion. Prophylactic antifungals as per institutional guidelines may be used at the physician's discretion at anytime. See Section 6.2.1.1, regarding the adjustment of dose for venetoclax in case of concomitant use of antibiotics and/or antifungals.

After the end of study treatment, all participants must be followed for adverse events (AEs) for 30 days; in addition, follow-up for AEs will be conducted for 150 days following the last dose of sabatolimab. All participants who discontinue study treatment will enter a long-term follow-up (for efficacy and/or survival status) as described in the study flow diagram below (Figure 3-2) and outlined in Section 9.1.

Figure 3-2 Study flow



The study flow is comprised of 3 study periods see (Figure 3-2): Pre-treatment (Screening), treatment and follow-up.

Participants will undergo safety and efficacy assessments during screening and periodically during treatment and follow-up as outlined in Section 8.1.

An end of treatment (EOT) visit will be performed when participants permanently discontinue study treatment. Participants will then enter safety/efficacy follow-up as shown in Figure 3-2 (see also Section 9.1.1).

All participants will be followed for survival as per Section 9.1.1.3.

4 Rationale

4.1 Rationale for study design

The overall study design, Phase II, single-arm, open-label, multi-center, is a design to evaluate safety, tolerability and efficacy of a novel combination. To avoid overdosing of sabatolimab in combination with azacitidine and venetoclax, the study does employ a two part design with a halt to enrolment between Part 1 (Safety run-in) and Part 2 (Expansion part). This design element allows, in Part 1, a Safety Review Meeting at each dose level, with evaluation of DLTs, and review of all available safety data to confirm that sabatolimab (400 mg and subsequently 800 mg Q4W) in combination with azacitidine and venetoclax, is safe, prior to opening enrollment to a larger participant population, in Expansion (Part 2). If the combination regimen with sabatolimab at 400 mg Q4W or 800 mg Q4W is not safe, the study will be stopped. A Steering Committee (Section 10.2.2) will be convened to review the safety during the entire course of study (Safety run-in (Part 1) and Expansion (Part 2)). The Expansion part and Cohort 2 (800 mg) will contribute to assess efficacy of the triple regimen (sabatolimab, venetoclax and azacitidine).

4.2 Rationale for dose/regimen and duration of treatment

Rationale for dose/regimen of sabatolimab

The study will start with cohort 1 (Part 1) of at least 3 evaluable participants treated with sabatolimab at a dose level of 400 mg Q4W in order to minimize the risk for unexpected toxicities of this novel combination of sabatolimab in combination with venetoclax and azacitidine. The proposed sabatolimab dose level for evaluation of efficacy in the study is 800 mg Q4W based on data accumulated from 2 phase I studies [CMBG453X2101], [CPDR001X2105], [CMBG453X2101] in solid tumor participants has a wide sabatolimab dose range. In sabatolimab single agent arms, sabatolimab doses ranged from 80 to 1200 mg every 2 weeks (Q2W) or every 4 weeks (Q4W), with a lower 20 mg Q2W sabatolimab dose additionally tested in combination with PDR001. Because of the data obtained in [CMBG453X2101], [CPDR001X2105] study started evaluating sabatolimab at 240 mg Q2W, 400 mg Q2W and 800 mg Q4W in combination with decitabine.

Clinical Pharmacology:

The pharmacokinetics (PK) of sabatolimab were similar between studies [CMBG453X2101] in solid tumor participants and [CPDR001X2105] in AML and high risk MDS participants. At lower doses (at 80 mg and below for Q2W dosing or at 240 mg and below for Q4W dosing),

the PK was nonlinear, with faster elimination at lower concentrations. PK appeared linear with an approximate proportional dose-exposure (AUC and Cmax) relationship at doses of 240 mg and above for Q2W dosing and at doses of 800 mg and above for Q4W dosing. Accumulation of sabatolimab was observed with repeated administrations, and for the Q2W regimen, AUCtau during cycle 3 ranged between 1.01-2.78 fold higher than during cycle 1. A dose of 800 mg Q4W has similar AUCtau as 400 mg Q2W at the steady state. As the dose of 800 mg Q4W is more convenient for the patients, it is the recommended dose for further development in MDS including the ongoing phase 3 trial [CMBG453B12301] and the present study.

Clinical Efficacy:

In study [CPDR001X2105], clinical benefit was seen across 3 dose levels tested (at 240 mg Q2W, 400 mg Q2W, 800 mg Q4W in combination with decitabine) with CR or marrow CR in high risk MDS participants and CR or CRi in newly diagnosed AML participants. Among participants that obtained CR, there were durable responses as long as 15 months (as of cut-off date of 10-Nov-2018). No obvious dose-response relationship was observed. In a preliminary exposure-response analysis, there was also no clear relationship between exposure and response, using a steady state exposure metrics of AUCtau or Ctrough and efficacy metrics of clinical benefit (CR/mCR/CRi) or percent of blast reduction.

Clinical Safety:

Sabatolimab was found to be safe and well tolerated across all dose levels tested in both studies. In study [CMBG453X2101], as of 09-Mar-2020, a total of 133 participants with solid tumors have been treated with sabatolimab single agent therapy. There were no adverse events attributed to study treatment with an incidence >10%. The most frequently reported adverse events attributed to study treatment included fatigue (9%), followed by nausea (5%) and decreased appetite (4%). There were no DLTs during the first cycle. No participants discontinued study treatment due to treatment-related AEs.

In study [CPDR001X2105], as of 10-Apr-2020, a total of 156 participants with hematological malignancies have been treated with sabatolimab as a single agent (n=26) or in combination with decitabine (n=82) or azacitidine (n=48). In the 26 participants treated with sabatolimab single agent, there were no adverse events attributed to study treatment with an incidence >10%. The most frequently reported adverse events attributed to study treatment were diarrhea and rash in two participants (8%), each. All other adverse events attributed to study treatment were single occurrences. There were no DLTs during the first cycle. No participants discontinued study treatment due to treatment-related AEs. In the 82 participants treated with sabatolimab in combination with decitabine, the most frequent adverse events (all grades, >10%) attributed to study treatment have included thrombocytopenia, anemia, neutropenia, nausea, and fatigue. One participant experienced a DLT during the first 2 cycles, which consisted of hepatitis manifesting as Grade 3 ALT increase. One participant discontinued study treatment due to a treatment-related AE of possible hemophagocytic lymphohistiocytosis. In the 48 participants treated with sabatolimab in combination with azacitidine, the most frequent adverse events (all grades, >10%) attributed to study treatment have included nausea, vomiting, anemia, constipation, neutrophil count decrease (and neutropenia), platelet count decrease (and thrombocytopenia), and fatigue. There were no DLTs during the first 2 cycles. No participants

discontinued study treatment due to treatment-related AEs. No study treatment-related deaths were observed in any of the studies mentioned above.

In study [CMBG453C12201], results from the first cohort of the safety run-in indicate sabatolimab 400 mg Q4W to be safe when administered in combination with azacitidine and venetoclax. A total of five adult participants with AML unfit for intensive chemotherapy were enrolled in that cohort, and a safety review meeting was conducted per the study protocol. No DLTs, deaths, or discontinuations due to AEs were reported. The overall safety profile of these 5 participants on triplet combination was generally consistent with that of venetoclax+ azacitidine. At the time of a data cut-off for the safety review meeting, two participants had discontinued study treatment; one participant achieved CR and discontinued after treatment cycle 2 to receive HSCT, and one participant discontinued due to disease progression. The remaining 3 participants were observed for at least 2 treatment cycles and study treatment was ongoing. The safety review concluded it was permissible to start enrollment in cohort 2 and to treat participants with sabatolimab at the dose level of 800 mg Q4W in combination with azacitidine and venetoclax.

Preliminary analysis revealed no relationship between dose, incidence and severity of adverse events across the different treatment groups. No relationship was observed between Cmax and the incidence of potentially immune related adverse events, providing additional support for 800 mg Q4W regimen, which has the highest Cmax among the doses tested. Please refer to the [Investigator's Brochure] for additional information of AEs reported in participants with solid tumors or with hematologic malignancies treated with sabatolimab as a single agent or in combination with other drugs.

Predicted Target Engagement:

A population pharmacokinetic model of sabatolimab concentration was fit to all participants from both studies. This model was used to simulate the TIM-3 occupancy in the bone marrow by making assumptions about sabatolimab biodistribution to the bone marrow and binding affinity to TIM-3. Using trial simulation, this model predicted that the 800 mg Q4W dose would give at least 95% receptor occupancy in at least 95% of participants at steady state Ctrough. This high degree of target engagement is also supported by a plateau in the accumulated soluble TIM-3 that is observed at doses of 240 mg Q2W and above, and at 800 mg Q4W and above.

In summary, given the excellent safety and tolerability seen across all doses and schedules in [CMBG453X2101] and [CPDR001X2105], the activity seen at all three doses tested in study [CPDR001X2105]; the predicted saturation of TIM-3 from the soluble TIM-3 data and the receptor occupancy model; and the lack of clear dose-response or exposure-response relationship for sabatolimab, 800 mg Q4W was selected as the target dose regimen for this study.

4.3 Rationale for choice of combination drugs

Rationale for combining sabatolimab with azacitidine and venetoclax

Venetoclax in combination with azacitidine or decitabine or low dose cytarabine has recently received approval from FDA (on 16-Oct-2020) in AML based on efficacy and safety, demonstrated in two open-label trials (see Section 1.1). Based on these trial results, venetoclax in combination with HMA is emerging as a potential new standard of care in this indication.

[redacted]

Furthermore, preliminary data indicate that venetoclax in combination with azacitidine is feasible, safe in MDS participants and associated with encouraging signs of efficacy. Ramp-up of venetoclax in AML and CLL is necessary; as in these indications are associated with high tumor burden, rapid death leukemic cells at the initiation of therapy and occurrence of TLS is frequent (Cairo and Bishop 2004). In contrast, ramp-up of venetoclax in MDS is not necessary based on the fact that risk of TLS in MDS is extremely low (Cairo and Bishop 2004) and also based on Phase Ib and retrospective studies findings, where ramp-up was not required, indicating absence of clinical TLS (Wei et al 2019, Ball et al 2020, Azizi et al 2020). Nevertheless, the participants enrolled in the Safety run-in part, will be hospitalized at Cycle 1 for 3 days to monitor the risk of TLS, See Section 3.

The rationale for combining sabatolimab with azacitidine and venetoclax is based on the following:

Emerging data suggest that immunotherapy may be a novel and promising therapeutic approach in higher-risk MDS, a disease with an important unmet medical need. However, the optimal immunotherapy has yet to be defined, and to date PD-1 inhibitors have demonstrated minimal single-agent activity, suggesting exploration of alternative approaches.

TIM-3 is a checkpoint inhibitor that plays a complex role in the negative regulation of innate and adaptive immune responses. Further, TIM-3 is expressed on leukemic stem cells and leukemic progenitor cells but not on normal hematopoietic stem cells. This suggests that TIM-3 inhibition by sabatolimab (MBG453) may have immunomodulatory as well as direct anti-leukemic effects.

Hypomethylating agents induce broad epigenetic effects including downregulating genes involved in cell cycle, cell division and mitosis, and upregulating genes involved in cell differentiation. However, these potentially anti-leukemic effects are accompanied by increased expression of TIM-3 as well as PD-1, PD-L1, PD-L2 and CTLA4, potentially downregulating immune-mediated anti-leukemic effects. These later effects justify the exploration of novel checkpoint inhibitors to decrease an immunosuppressive tumor microenvironment (Yang et al 2014, Ørskov et al 2015).

Venetoclax is an inhibitor of BCL-2. BCL-2 inhibits apoptosis of factor-deprived cells, but does not prevent apoptosis of immune cell mediated killing, indicating different mechanisms of apoptosis induction (Vaux et al 1992). Therefore, blockage of both BCL2, which promotes direct leukemic cell apoptosis, and TIM-3, which may promote both immune cell mediated killing and direct leukemia-stem cell targeting, may induce cancer cell elimination via different pathways and possibly create a synergistic effect.

Study [CPDR001X2105] has demonstrated that sabatolimab can be administered safely in combination with an HMA, decitabine, and that this combination demonstrates preliminary efficacy including durable responses in participants with AML and high-risk MDS (see Section 4.2).

Further, as a mAb, sabatolimab is not metabolized by cytochrome P450 (CYP450) enzymes, or transported by P-glycoprotein (Pgp) or related ABC membrane transporters, therefore an impact of DDIs on the PK of sabatolimab by azacitidine, or venetoclax is not anticipated. Cytokines produced by activated lymphocytes may impact the levels of Pgp and the activity of CYP450

enzymes (Renton 2005, Dumais et al 2008, Harvey and Morgan 2014); the clinical relevance to sabatolimab is unknown. However, preliminary data from the clinical study [CPDR001X2105], which has shown that the co-administration of sabatolimab with decitabine did not result in changes in their PK parameters. Therefore, a clinically relevant DDI effect is considered unlikely.

Taken together, these data suggest that the combination of sabatolimab, venetoclax and azacitidine, can be administered safely with little overlapping toxicity contributed by sabatolimab, and that sabatolimab may improve the efficacy of azacitidine and venetoclax.

4.4 Rationale for MRD assessment [redacted]

4.4.1 Rationale for MRD assessments

Minimal residual disease (MRD) in AML/higher risk MDS refers to the presence of leukemic cells at a sensitivity of detection below the threshold of conventional morphologic methods. Participants who experience a CR according to morphologic assessments (<=5% blast in the bone marrow), can potentially still harbor a large number of leukemic cells in the bone marrow which can confer a poor outcome. Detection of MRD in AML has shown prognostic relevance in several studies (Freeman et al 2013, Terwijn et al 2013, Ivey et al 2016, Jongen-Lavrencic et al 2018, Freeman et al 2018), indicating that depth of leukemic clearance should be considered as a relevant prognostic endpoint in this setting. While the majority of MRD studies to date have focused on AML participants, higher risk MDS participants have been included in some of the participants cohorts (Freeman et al 2013, Freeman et al 2018), since detection of MRD in this setting is likely to yield similar prognostic value. Consistently, post-transplant MRD positivity predicted relapse in higher risk MDS participants (Mo et al 2016).

[redacted]

4.5 Purpose and timing of interim analyses/design adaptations

No formal interim analyses are planned (see Section 12.7).

However, the study design foresees that during and at the conclusion of Part 1 (Safety run-in), decisions based on emerging data are taken at safety review meetings following completion of enrollment at each dose level (or earlier if required) and prior to starting the Expansion (Part 2). At the Safety Review Meetings, the decision to escalate to the 800 mg Q4W dose level or to open the Expansion part at the sabatolimab dose level of 800 mg Q4W will be guided by a Bayesian analysis based on the incidence of dose limiting toxicity (DLT) data, and supported by all available data, including safety data, clinical pharmacology data, tolerability data, and recommendations from participating investigators. The decision to enroll further participants at the sabatolimab 800 mg Q4W in the Safety run-in part and to open Part 2 (Expansion Part) to enrollment, will be communicated to investigators.

Details of this procedure and the process for communication with investigators are provided in Section 6.5.1.

The primary analysis on CR rate (Expansion (Part 2)) will be performed after all participants have completed at least 6 cycles of treatment with sabatolimab + azacitidine + venetoclax (see Section 12.7).

4.6 Risks and benefits

Venetoclax in combination with azacitidine, decitabine, or low-dose cytarabine has been approved by the FDA in 16-Oct-2020 to treat newly-diagnosed AML in adults 75 years or older,

or who have comorbidities precluding intensive induction chemotherapy. Venetoclax was initially granted accelerated approval for AML in Nov-2018.

Findings from a Phase Ib (Wei et al 2019) and retrospective clinical evaluation of venetoclax in combination with azacitidine suggested promising efficacy results in higher-risk MDS participants (Ball et al 2020, Azizi et al 2020).

The potential benefit of sabatolimab combined with HMA in MDS is suggested by early efficacy results from the study [CPDR001X2105], which showed achievement of durable complete remission or bone marrow CR in high risk MDS participants receiving sabatolimab in combination with HMA. The proportion of higher-risk MDS participants achieving CR/mCR and durable CR/mCR under treatment with sabatolimab combined with HMA appears to be larger as compared to historic and published data on similar MDS participants treated with HMA alone. As of 25-Jun-2020, among 35 evaluable participants with HR-MDS who were treated with sabatolimab in combination with HMA, the overall response rate (ORR) was 62.9%: 8 complete remissions (CR), 8 marrow CR (5 with hematologic improvement [HI]), 6 stable diseases with HI. Median time to response was 2.0 months and estimated 6-months duration of response rate for CR/mCR/PR was 90% (95% CI: 73.2-100%).

The risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring. Further, dose modifications are provided and must be applied per protocol based on clinical or laboratory findings (see Section 6.5.3).

Occurrence of an immune-related adverse event is an anticipated risk in participants treated with immune-oncology drugs such as sabatolimab. In the case of an immune-related event, there are dose modification and management guidelines, including detailed plans for follow-up of toxicities. In addition, the protocol references and will adhere to recent American Society of Clinical Oncology (ASCO) practices guidelines for management of immune-related adverse events in participants treated with checkpoint inhibitors (Brahmer et al 2018) (see Section 6.5.3 and Section 6.5.4.1).

Based on currently available data, there are no known significant overlapping toxicities between the combination of venetoclax and azacitidine and sabatolimab. However, this novel combination treatment may have unforeseen risks, which could be serious. In particular, there is the potential for increased toxicity secondary to cytokine release syndrome due to activation of T cells and macrophages, and there may also be changes in immune function that could lead to autoimmunity or other immune-related adverse events as well as increased risk of infection. All participants enrolled will be monitored closely for these potential toxicities.

Furthermore, as the safety of sabatolimab administered in combination with azacitidine + venetoclax has not been assessed previously, the protocol stipulates that consecutive Safety run-in cohorts at 400 mg Q4W and 800 mg Q4W (Part 1) will be observed for at least 2 treatment cycles followed by a Safety Review Meeting, before opening enrollment to a larger participant population in Part 2 (Expansion). A Steering Committee (see Section 10.2.2) will review the safety data during the course of the study including at the time of the two safety reviews planned during the Safety run-in.

Women of childbearing potential and sexually active males 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 until at least 30 days after the last dose of venetoclax, 90 days after the last dose of azacitidine, and 150 days after the last dose of sabatolimab, whichever is later. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

No substantial additional risk for participants' safety due to the SARS-CoV-2 virus and the COVID-19 pandemic has been identified at this time and therefore the benefit risk remains unchanged. In case of active COVID-19 infection, a careful benefit risk evaluation to be performed to determine whether participants can remain on study medication or not.

5 Study Population

The study population will include approximately 76 adult participants (i.e. approximately 18 participants in Safety run-in (Part 1) [including 6 participants in cohort 1, 12 participants in cohort 2] and approximately 58 participants in Expansion (Part 2) with high or very high risk (per IPSS-R prognostic risk categories) myelodysplastic syndromes. These participants have an indication for treatment with azacitidine in first-line setting and are not immediately eligible at the time of screening for intensive chemotherapy or HSCT according to medical judgment and local standard medical practice/institutional guidelines for treatment decisions.

The investigator or designee must ensure that only participants who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study
2. Age ≥ 18 years at the date of signing the informed consent form (ICF)
3. Morphologically confirmed diagnosis of myelodysplastic syndrome (MDS) based on 2016 WHO classification (Arber et al, 2016) by local investigator assessment with one of the following Prognostic Risk Categories, based on the revised International Prognostic Scoring System (IPSS-R) (Greenberg et al 2012):
   - Very high (> 6 points)
   - High (> 4.5-6 points)
4. Not immediately eligible for hematopoietic stem-cell transplantation (HSCT) or intensive chemotherapy at the time of screening due to individual clinical factors such as age, comorbidities and performance status, donor availability (de Witte et al 2017)
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2
6. Indication for azacitidine treatment according to the investigator, based on local standard medical practice and institutional guidelines for treatment decisions

[redacted]

7. AST and ALT ≤ 3 × upper limit of normal (ULN)
8. Total bilirubin ≤ 1.5 × ULN (except in the setting of isolated Gilbert syndrome, where participants may only be included with total bilirubin ≤ 3.0 x ULN)
9. Estimated Glomerular Filtration Rate (eGFR) ≥ 30 mL/min/1.73 m^2 (estimation based on Modification of Diet in Renal Disease) (MDRD) formula, by local laboratory)
10. Participant is able to communicate with the investigator, and has the ability to comply with the requirements of the study procedures

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. Prior exposure to TIM-3 directed therapy or any BCL-2 inhibitor (including venetoclax) at any time.
2. Prior therapy with immune check point inhibitors (e.g. anti-CTLA4, anti-PD-1, anti-PD-L1, or anti-PD-L2) or cancer vaccines is not allowed if the last dose of the drug was administered within 4 months prior to start of treatment.
3. Previous first-line treatment for very high risk or high risk myelodysplastic syndromes (based on IPSS-R, Greenberg et al 2012 and Arber et al, 2016) with any antineoplastic agents, approved or investigational, including chemotherapy, lenalidomide and hypomethylating agents (HMAs) such as decitabine or azacitidine.
   However, a single cycle of HMAs treatment only started prior to enrollment is allowed.
4. Live vaccine administered within 30 days prior to start of treatment
5. Current use or use within 14 days prior to start of treatment of systemic steroid therapy (> 10mg/day prednisone or equivalent) or any immunosuppressive therapy. Topical, inhaled, nasal, ophthalmic steroids are allowed. Replacement therapy, steroids given in the context of a transfusion are allowed and not considered a form of systemic treatment
6. History of severe hypersensitivity reactions to any ingredient of study drug(s) (azacitidine, venetoclax or sabatolimab) or monoclonal antibodies (mAbs) and/or their excipients
7. Participants with myelodysplastic syndrome (MDS) based on 2016 WHO classification (Arber et al, 2016) with revised International Prognostic Scoring System (IPSS-R) ≤ 4.5
8. Diagnosis of acute myeloid leukemia (AML) including acute promyelocytic leukemia and extra-medullary acute myeloid leukemia based on WHO 2016 classification (Arber et al, 2016)
9. Diagnosis of therapy-related MDS based on WHO 2016 classification (Arber et al, 2016)
10. Diagnosis of chronic myelomonocytic leukemia (CMML), MDS/MPN or primary or secondary myelofibrosis based on 2016 WHO classification (Arber et al, 2016)
11. History of organ transplant or allogenic hematopoietic stem cell transplant
12. Any concurrent severe and/or uncontrolled medical condition e.g., any active systemic infection, or any severe and/or uncontrolled infection requiring parenteral anti-infectives

including antibacterial, antiviral or antifungal therapy (such as severe pneumonia, meningitis, or septicemia)

13. Participants with prior malignancy, **except:**

    a) Participants with history of intermediate risk MDS or lower risk MDS treated by any supportive care (e.g. growth factors, TGF'beta agents) or untreated are eligible

    b) Participants with history of intermediate or lower risk MDS who were treated adequately with lenalidomide and then failed are eligible

    c) Participants with history of adequately treated malignancy for whom no systemic anti cancer therapy (namely chemotherapy, radiotherapy or surgery) is ongoing or required during the course of the study. Subjects who are receiving adjuvant therapy such as hormone therapy are eligible. However, subjects who developed therapy-related MDS are not eligible (see exclusion criterion 9).

14. Cardiac or cardiac repolarization abnormality, including but not limited to any of the following:

    a) History of myocardial infarction (MI), angina pectoris, or coronary artery bypass graft (CABG) within 6 months prior to starting study treatment

    b) QTcF > 470 ms at screening, long QT syndrome or family history of unexplained cardiac death

    c) Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block)

15. Sexually active males unless they use a condom during intercourse while taking azacitidine and for 3 months after stopping the drug. They should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

    In addition, male participants must not donate sperm for the time period specified above.

16. Participant is pregnant or breastfeeding

17. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during study treatment and for at least one month after the last dose of venetoclax, 3 months after the last dose of azacitidine (or as per their respective local labels, whichever is longer) and 150 days after the last dose of sabatolimab. Highly effective contraception methods include:

    - Total abstinence (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 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

[redacted]

- Male sterilization (at least 6 months prior to screening/baseline). For female participant on the study the vasectomized male partner should be the sole partner
- Use of oral (estrogen and progesterone), injected or implanted combined hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. It is currently unknown whether venetoclax may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method.

In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal and not of childbearing potential if they have had over 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate , history of vasomotor symptoms) in the absence of other medical justification or have had surgical bilateral oophorectomy (with or without hysterectomy) or bilateral tubal ligation at least 6 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 childbearing potential.

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

18. Human immunodeficiency virus (HIV) infection not controlled by standard therapy and/or with known history of opportunistic infection. For countries where HIV status is mandatory: testing positive for HIV during screening using a local test
19. Active Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection. Participants whose disease is controlled under antiviral therapy may be eligible
20. Other co-morbidity that, in the opinion of the investigator, predisposes the participant to high risk of noncompliance with the protocol
21. Participant has consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Starfruit within 3 days prior to the initiation of study treatment (C1D1)

6 Treatment

6.1 Study treatment

In this study, the term “investigational drug” refers to the Novartis study drug, sabatolimab. The term "study treatment” refers to the combination of study drugs: sabatolimab plus venetoclax plus azacitidine.

All dosages prescribed, dispensed to the participant and all dose changes during the study including the reason for any component of the study treatment must be recorded on the appropriate eCRF page.

[redacted]

6.1.1 Investigational and control drugs

Table 6-1 Study Treatment

Investigational/ Combination Drug (Name and Strength)	**Strength**	**Pharmaceutical dosage form and route of administration**	**Supply Type**	**Sponsor (global or local)**
Sabatolimab	400 mg/4 ml	solution in vial for i.v. infusion	Open Label	Sponsor (global)
Venetoclax	100 mg and/or 50 mg and/or 10 mg	tablet for oral use	Open Label	Sponsor (global/local)
Azacitidine*	100 mg / vial	powder for suspension for injection or powder for solution for infusion for subcutaneous use or intravenous use	Open Label	Sponsor (global/local)

*formulation for generic azacitidine as approved by local regulations

Sabatolimab

Sabatolimab will be administered at a dose of 400 mg Q4W (Safety run-in (Part 1) cohort 1) or 800 mg Q4W (Safety run-in (Part 1) cohort 2 and Expansion (Part 2)) via i.v. infusion over 30 minutes on Day 8 of every 28-day cycle.

If the alternative schedule is selected for azacitidine by the investigator, azacitidine and sabatolimab will be given on the same day (Day 8 of the 28-day cycle). Azacitidine should be administered first, followed by sabatolimab.

Further instructions for the preparation, dispensation and administration of sabatolimab are described in the Pharmacy Manual.

Venetoclax

Venetoclax film-coated tablets should be administered at a dose of 400 mg orally or corresponding reduced dose for concomitant use with P-gp inhibitors or moderate or strong CYP3A4 inhibitors (see Table 6-2 and Venclexta® (Venclexta® (Venetoclax) USPI (2020)), once a day, from C1D1 to C1D14 during the 28-day cycle. Participants should be instructed to

[redacted]

swallow the tablets whole (tablets should not be crushed or broken), with water, at approximately the same time each day. The tablets should be taken with a meal (ideally at breakfast). No ramp-up for venetoclax is necessary, See Section 3, Section 4.3 and Section 6.5.4.2.

A reduced dose of venetoclax per day for concomitant use with P-gp inhibitors or moderate or strong CYP3A4 inhibitors (see Table 6-2 and Venclexta® (Venclexta® (Venetoclax) USPI (2020)) is necessary. In particular, many antifungals (e.g. posaconazole) and antibiotics, frequently used for prophylaxis or treatment of infection, are strong or moderate CYP3A4 inhibitors and their use should lead to dose adjustment of venetoclax as indicated in Table 6-2.

If a participant misses doses of venetoclax within 8 hours of the time it is usually taken, the participant should take the missed dose as soon as possible on the same day. If the participant misses a dose by more than 8 hours, the participant should not take the missed dose and should resume the usual dosing schedule at the usual time the following day. If a participant vomits after taking venetoclax, the dose should not be re-administered and the participant should take their next dose at the usual time the following day.

On the days of PK sampling, the participant will be instructed to bring his/her drug supply to the site, and take the dose in the clinic, under supervision of the site personnel. The exact time for dose administration and breakfast (if applicable) intake must be recorded in the source documents and electronic Case Report Form (CRF).

Azacitidine

Azacitidine is considered as a Standard of Care in the population enrolled in this study and it should be administered according to standard local clinical practice. A standard dose of azacitidine (75 mg/m^2) will be given subcutaneously or intravenously every day for seven consecutive days on days 1-7 out of a 28 days cycle (see local azacitidine package insert). In keeping with standard clinical practice, the alternative schedules of 75 mg/m^2 for five consecutive days on days 1-5, followed by a two day break, then two consecutive days on days 8-9 will be permitted (alternative schedule).

Azacitidine regimen used in this protocol were selected because they are the most studied regimens and recommended by international treatment guidelines (NCCN, ESMO) (Fey and Buske 2013, O'Donnell et al 2017).

NOTE: On days of co-administration of venetoclax, azacitidine and sabatolimab, please refer to the Pharmacy Manual for instructions.

6.1.2 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

6.1.3 Treatment arms/group

Not applicable.

[redacted]

6.1.4 Guidelines for continuation of treatment

Per protocol, dose modifications, including dose interruptions, for toxicities are permitted and are outlined in Section 6.5.

6.1.5 Treatment duration

A participant may be discontinued from study treatment for reasons of unacceptable toxicity, progressive disease (including transformation to leukemia per WHO 2016 classification) or relapse, HSCT, intensive chemotherapy, withdrawal of consent by the participant, pregnancy, failure to adhere the protocol or at the discretion of the investigator or if the study is terminated by the Sponsor.

Patients who complete participation in this trial and continue to derive clinical benefit from the treatment based on the investigator's evaluation may receive post-trial access. Post Trial Access (PTA) means the provision of investigational treatment to trial participants following their completion of trial participation. PTA will be provided until one of the following is met: participant no longer derives clinical benefit, investigator discontinues treatment, launch or reimbursement (where applicable), treatment fails to achieve registration in the trial participant's country, or the clinical program is discontinued for any other reason.

Mechanisms for provision of PTA may include an extension phase to this study, a separate extension protocol, a rollover protocol, provision of the Novartis investigational product in a non-trial setting (known as post-study drug supply [PSDS]) when no further safety or efficacy data are required, or any other mechanism appropriate for the country.

The PTA mechanism must comply with local laws and regulations in the participating trial countries. If Novartis discontinues the PTA for this trial, Novartis will work with investigators to transition patients onto locally available alternative treatment, or standard of care.

6.1.5.1 Treatment beyond disease progression

Treatment beyond disease progression is not permitted.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

In general, the use of any concomitant medication/therapy deemed necessary for the care of the participant (e.g., such as antibiotics, antifungals, anti-emetics, anti-diarrheal) is permitted (see Section 6.2.1.1), except when specifically prohibited (see Section 6.2.2). Prophylaxis with antibiotics as per local institutional guidelines is mandatory at Cycle 1 and thereafter this type of prophylaxis may be used per investigator's discretion. Prophylaxis antifungals, as per institutional guidelines, is allowed at anytime. In case of concomitant medications (e.g antibiotics, antifungals), dose adjustment of venetoclax may be necessary, as indicated below. The participant must be told to notify the investigational site about any new medications he/she takes after the start of the study treatment.

Participants should not receive pre-medication to prevent infusion reaction before the first infusion of sabatolimab. If a participant experiences an infusion reaction, he/she may receive

[redacted]

pre-medication on subsequent dosing days. The pre-medication should be chosen per institutional standard of care, at the discretion of the treating physician.

Acute allergic reactions should be treated as needed per institutional standard of care. In the event of anaphylactic/anaphylactoid reactions, this includes any therapy necessary to restore normal cardiopulmonary status. If a participant experiences a Grade ≥ 3 anaphylactic/anaphylactoid reaction, the participant will be discontinued from the study treatment (see Section 6.5.3 for guidance).

Sabatolimab should be administered in a facility equipped for cardiopulmonary resuscitation. Appropriate resuscitation equipment should be available, and a physician readily available.

Participants should receive appropriate prophylaxis (e.g. antiemetics) for azacitidine as per local practice.

All medications, procedures, and significant non-drug therapies including physical therapy and blood transfusions received within 16 weeks before the first dose of study treatment is administered, during the course of the study and until the end of efficacy follow-up, should be recorded in the appropriate Case Report Forms (see Table 8-1).

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medications and local prescribing information of azacitidine (Vidaza® (Azacitidine) USPI (2008)) and venetoclax (Venclexta® (Venetoclax) USPI (2020)). If in doubt, the investigator should contact the Novartis medical monitor before a participant starts treatment or allowing a new medication to be started. If the participant has already started treatment, contact Novartis medical monitor to determine if the participant should continue study treatment. Supportive therapy including prophylactic antibiotic and antifungal treatments, transfusions, growth factors (e.g. GCSF, ESA) etc. will be administered at the discretion of the investigators according to their local standard of care.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Medications to be used with caution during study treatment in this study are listed below. Please also refer to Appendix 2 (see Section 16.2) for detailed guidance.

Strong or moderate CYP3A4 inhibitors and P-gp inhibitors: If, such therapy is necessary, it can be introduced, under the provision that the dose of venetoclax is reduced. Recommendation for venetoclax dose, when given in combination with strong CYP3A inhibitors (e.g., posaconazole, ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, lopinavir, ritonavir, telaprevir, and voriconazole), moderate CYP3A inhibitors (e.g., erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, and verapamil) or P-gp inhibitors (e.g., amiodarone, azithromycin, captopril, carvedilol, felodipine, quercetin, quinidine, ranolazine, and ticagrelor) are provided in Table 6-2 below.

Table 6-2 Management of potential interactions of CYP3A and P-gp inhibitors with venetoclax

Concomitant drug	Dose Reduction
Posaconazole	Reduce venetoclax dose to 70 mg

Other strong CYP3A inhibitor	Reduce venetoclax dose to 100 mg
Moderate CYP3A inhibitor or P-gp inhibitor	Reduce venetoclax dose to 200 mg

The venetoclax dosage that was used prior to concomitant use with a strong or moderate CYP3A inhibitor or a P-gp inhibitor should be resumed 2 to 3 days after discontinuation of the inhibitor. Participants should be instructed to avoid grapefruit products, Seville oranges, and starfruit during treatment with venetoclax as they contain inhibitors of CYP3A4.

Strong or Moderate CYP3A4 inducers: Concomitant use of venetoclax with strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, St.John's wort) or moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) should be avoided. Alternative treatments with less CYP3A induction should be considered.

P-gp or BCRP substrates: Co-administration of narrow therapeutic index P-gp, or BCRP substrates (e.g., digoxin, sirolimus) with venetoclax should be avoided.

If a narrow therapeutic index P-gp or BCRP substrate must be used, it should be used with caution. For an orally administered P-gp or BCRP substrate sensitive to inhibition in the gastrointestinal tract (e.g., dabigatran etexilate), its administration should be separated from venetoclax administration as much as possible to minimize a potential interaction.

Anticoagulation therapy is permitted if the participants are already at stable dose of warfarin or stable doses of low molecular weight heparin (LMWH) for > 2 weeks at time of first dose and International Normalized Ratio (INR) should be monitored closely. Participants who develop a new requirement for anticoagulant therapy during the conduct of the study may remain on study after documented discussion with the Novartis medical monitor. However, ongoing anticoagulant therapy should be temporarily discontinued to allow bone marrow sampling according to the institutional guidelines.

Anti-hypertensive therapy is allowed as concomitant medications; however because transient hypotension has occurred during infusions of monoclonal antibodies, consideration should be given to withholding anti-hypertensive medications for 12 hours prior to infusion with sabatolimab.

6.2.2 Prohibited medication

During the course of the study, participants must not receive additional investigational drugs, devices, chemotherapy, or any other therapies that may be active against cancer or modulate the immune response.

The use of systemic steroid therapy at immunosuppressive dose (> 10 mg/day of prednisone or equivalent) and other immunosuppressive drugs are not allowed except for the treatment of infusion reaction, immune related adverse events (irAEs), for prophylaxis against imaging contrast dye allergy or in the context of transfusion, for replacement-dose steroids in the setting of adrenal insufficiency or for treatment of transient exacerbation of other underlying diseases such as chronic obstructive pulmonary disease requiring treatment for ≤ 3 weeks.

[redacted]

Systemic corticosteroids required for control of infusion reactions or irAEs must be tapered and be at non-immunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next sabatolimab administration.

If more than 10 mg/day prednisone is used, sabatolimab should be temporarily interrupted until the participant receives 10 mg/day or less of prednisone.

Topical, inhaled, nasal and ophthalmic steroids are allowed.

The use of live vaccines are not allowed through the duration of the study treatment and 150 days after the last dose of sabatolimab. Inactivated vaccines, subunits recombinant, polysaccharide and conjugate vaccines and toxoid vaccines are allowed.

Vaccination against COVID-19, unless these are live vaccines, is allowed during screening and during the treatment phase but should not be administered on the same day of study treatment administration to avoid potential overlapping adverse events.

In addition, prohibited medication related to azacitidine and venetoclax will apply according to local label.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a participant Number (participant No.) that is assigned when the participant is first enrolled for screening and is retained as the primary identifier for the participant, unless 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 is numbered uniquely across the entire database. Upon signing the informed consent form, the site will use the electronic data capture system to assign the participant the next sequential participant No.

The investigator or designated staff will contact the Interactive Response Technology (IRT) and provide the requested identifying information to register the participant. Once assigned, the participant No. must not be reused for any other participant and the participant No. for that individual must not be changed, unless the participant is re-screened. If the participant fails to start treatment for any reason, the reason will be entered into the appropriate eCRF page and IRT should be notified as soon as possible. Re-screening is allowed once for participants that were initially screen failures for any reason. All eligibility criteria must be re-checked and met prior to enrollment of the participant into the study. A new participant No. should be assigned for all re-screened participants.

6.3.2 Treatment assignment, randomization

This study is open label and non-randomized.

Prior to dosing at Cycle 1 Day 1, participants who fulfill all the inclusion/exclusion criteria will be enrolled via IRT and a treatment number will be provided for the study treatments sabatolimab, venetoclax, and azacitidine.

The Investigator (or delegate) will call or log on to the IRT and confirm that the participant fulfills all the inclusion/exclusion criteria by completing the eligibility criteria checklist embedded in the system. The IRT will assign a unique medication number for the first package of study treatments to be dispensed to the participant.

6.4 Treatment blinding

The study is open-label with no blinding.

6.5 Dose escalation and dose modification

Two dose levels of sabatolimab, 400 mg Q4W (Safety run-in (Part 1) cohort 1) and 800 mg Q4W (Safety run-in (Part 1) cohort 2) will be evaluated. Intra-participant dose escalation is not permitted. Guidance for dose modifications is provided in Section 6.5.1.

6.5.1 Dose escalation guidelines

6.5.1.1 Sabatolimab dose level and regimen

Sabatolimab will be given at 400 mg every 4 weeks in the first approximately 6 enrolled participants (at least 3 evaluable participants) (cohort 1 of the Safety run-in (Part 1)). If this dose level is considered safe, sabatolimab will be given at 800 mg every 4 weeks in the next approximately 12 participants (at least 9 evaluable participants) (cohort 2 of the Safety run-in (Part 1)).

In case the combination does not meet overdose criteria at the cohort 1 of Safety the run-in (Part 1) (participants treated with sabatolimab at 400 mg Q4W); but meets the overdose criteria at cohort 2 of the Safety run-in (Part 1) (participants treated with sabatolimab at 800 mg Q4W), the Expansion (Part 2) will not be opened. The Expansion (Part 2) will be opened only if the two cohorts does not meet the overdose criteria consecutively.

6.5.1.2 Provisional dose levels

Table 6-3 below describes the starting dose and the dose levels that may be evaluated during the Safety run-in (Part 1) of this trial.

Table 6-3 Provisional dose levels of sabatolimab during Safety run-in (Part 1)

Dose level	Proposed dose* (Q4W)	Increment from previous dose
1	400 mg	(starting dose)
2	800 mg	100%

* In combination with azacitidine (75 mg/m^2 Day 1-7) + venetoclax (400 mg Day 1-14)

6.5.1.3 Guidelines for assessing tolerability

For the purpose of assessing the risk of overdosing (as defined by EWOC criterion, see details below) of sabatolimab in combination with azacitidine and venetoclax, at each sabatolimab dose level, after the required number of evaluable participants, at least 3 participants for cohort 1

(Part 1) and at least 9 participants for cohort 2 (Part 1), have been included, and observed for at least 2 cycles, a safety review meeting will be conducted.

Participant will be considered evaluable for DLT if:

· Participant has received 2 infusions of sabatolimab at the assigned dose level in Q4W dosing regimen, and has taken at least 75 % of the planned dose of azacitidine and venetoclax (i.e. for 2 cycles: 11 doses of azacitidine out of the 14 doses planned and 21 doses of venetoclax out of the 28 doses planned), and participant has had safety assessments for a minimum period of 2 cycles (from Cycle 1 Day 1 to the end of Cycle 2). Participants receiving a reduced dose of venetoclax due to co-administration of strong or moderate CYP3A4 inhibitors or P-gp inhibitors as described in Table 6-2, will be considered to have received the planned dose.

or

· Participant has experienced a DLT within the DLT observation period from first dose of sabatolimab to the end of Cycle 2. Note that participants who experience toxicity that meets the criteria for DLT but occurs prior to the first dose of sabatolimab will be considered not evaluable.

At the Safety Review Meetings, Investigators and Novartis study personnel will review all relevant data available from the ongoing study including safety information, DLTs, time of occurrence of DLT, supported by all CTCAE v5.0 ≥ Grade 2 toxicity data during the first 2 cycles of the study treatment, and pharmacokinetic data from evaluable participants.

The decision will be guided by a Bayesian model with EWOC principle evaluating the probability of DLT. For each cohort of the Safety run-in, the probability of excessive toxicity (i.e. DLT rate ≥ 33%) will be assessed after the required number of evaluable participants have been treated and observed for up to end of Cycle 2. If the EWOC criteria is satisfied (probability of excessive toxicity is lower than 25%), the Bayesian model will recommend to start enrollment to either cohort 2 (Part 1) or the Expansion Part (Part 2).

At the safety review meetings, the available toxicity information (including adverse events and laboratory abnormalities that are not DLTs), the time (days from start of therapy) of occurrence of DLT, the recommendations from the Bayesian analysis, and the available PK and pharmacodynamic information will all be evaluated by the Investigators and Novartis study personnel. Once the results of the safety review meeting are available, the investigator will receive written confirmation from Novartis indicating that the results of the Safety run-in part (Part 1) were evaluated and that it is permissible to start enrollment to either cohort 2 (Part 1) or the Expansion Part (Part 2).

6.5.2 Definitions of dose limiting toxicities (DLTs)

Dose-limiting toxicities will be collected and evaluated in participants enrolled to the Safety run-in part. A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value considered by the Investigator to be at least possibly related to sabatolimab as a single contributor or in combination with other component(s) of study treatment that occurs during the DLT observation period and meets any of the criteria included in Table 6-4. The DLT observation period is Cycle 1 Day 8 (starting from the first infusion of sabatolimab) to the

end of Cycle 2. The National Cancer Institute Common Terminology Criteria for Adverse events (NCI CTCAE) version 5.0 will be used for all grading.

If a participant experiences a DLT (during the DLT observation period) then study treatment must be interrupted and may be permanently discontinued depending on the severity of the DLT, if the DLT resolves to CTCAE Grade 1 or baseline value, the participant may continue to receive study treatment following consultation with the Novartis medical monitor.

The investigator must notify the sponsor immediately of any unexpected CTCAE grade ≥ 3 adverse events or laboratory abnormalities.

Table 6-4 Criteria for defining dose-limiting toxicities during the Safety run-in (Part 1)

Toxicity	DLT Criteria
Hematology	Because marrow suppression is an expected consequence of MDS and its therapy, for participants participating in this study, only persistent grade 4 neutropenia, thrombocytopenia and pancytopenia beyond Day 42 from the start of a study treatment cycle and is not related to the underlying disease will be considered to be a DLT (bone marrow evaluation may be required to determine if the bone marrow suppression is due to the underlying disease). OR Febrile neutropenia CTCAE Grade 4 OR Sepsis CTCAE Grade 4
Vascular disorders	Hypertension CTCAE Grade 3 persisting for > 7 days after treatment is administered, despite adequate antihypertensive therapy
General disorders and administration site conditions	Infusion reaction CTCAE Grade 3 that does not resolve to Grade 1 within 72 hours or CTCAE Grade 4 of any duration
Immune	Immune-related adverse events ≥ CTCAE Grade 3 persisting > 7 days after starting appropriate treatment* (e.g. with corticosteroids)
Occular	Eye pain or vision decreased:

Toxicity	DLT Criteria
	≥ CTCAE Grade 2 that does not improve to Grade 1 severity within 2 weeks after the initiation of topical therapy OR Eye pain or vision decreased that requires systemic treatment
Pulmonary	Pneumonitis of non infectious etiology ≥ CTCAE Grade 2 persisting > 7 days despite treatment with corticosteroids
	Pneumonitis of non infectious etiology ≥ CTCAE Grade 3
Skin and subcutaneous tissue disorders	Photosensitivity ≥ CTCAE Grade 3 for > 7 days after treatment
	Rash ≥ CTCAE Grade 3 for > 7 days after treatment
	Rash CTCAE Grade 4 Any severe skin reactions (such as Toxic Epidermal Necrolysis, Steven Jones Syndrome)
Gastrointestinal disorders	Diarrhea CTCAE Grade ≥ 3 ≥ 48 hrs., despite the use of anti-diarrhea therapy
	Nausea/ vomiting CTCAE Grade ≥ 3 ≥ 48 hrs., despite the use of anti-emetic therapy
	Pancreatitis CTCAE Grade ≥ 3
Investigations	Blood bilirubin increase ≥ CTCAE Grade 2 (caused by increased direct bilirubin) with ALT and/or AST ≥ CTCAE Grade 2, without evidence of cholestasis and with absence of any alternative cause likely explaining the combination of increased ALT or AST and blood bilirubin
Other	Other clinically significant toxicities, including a single event or multiple occurrences of the same event that lead to a dosing delay of > 7 days in cycle 1, or result

Toxicity	DLT Criteria
	in an inability to deliver ≥ 75% of the planned dose intensity for any of the study drugs in a cycle of treatment because of treatment-related toxicity.
	Any other unacceptable toxicity encountered by a participant as determined by the Investigators and Novartis.
	Any grade 4 non-hematologic toxicity that is not clearly related to a cause other than the study treatment under study.
Exceptions to DLT Criteria	
· Grade 3 fatigue, asthenia, fever, anorexia, or constipation · Grade 3 nausea, vomiting or diarrhea not requiring tube feeding, total parenteral nutrition, or prolonged hospitalization · Infection, bleeding, or other expected direct complication of cytopenias due to active underlying disease · Grade 3 or 4 tumor lysis syndrome if it is successfully managed clinically and resolves within 7 days without end-organ damage · Grade 3 or 4 isolated laboratory abnormalities that last ≤3 days	

*Unless otherwise specified for organ-specific immune-related DLTs · CTCAE version 5.0 will be used for all grading

6.5.3 Dose modifications

For participants who do not tolerate the protocol-specified dosing schedule: dose interruptions (for sabatolimab, azacitidine and venetoclax), and/or dose reductions (azacitidine and venetoclax only) are either recommended or mandated in order to allow participants to continue the study treatment. Dose reductions for sabatolimab are not allowed.

Guidelines for permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-5 and Table 6-6.

Dose interruption at the start of a new treatment cycle

In participants who have achieved CR or mCR and have Grade 4 neutropenia and/or Grade 4 thrombocytopenia dosing of both venetoclax and azacitidine should be interrupted until resolution to ≤ Grade 2. Sabatolimab should not be administered during the dose interruption. After resolution, dosing of both azacitidine and venetoclax should be resumed on the same day with dose modification for venetoclax as specified in Table 6-6. The first day dosing is resumed will be considered as D1 of the new treatment cycle and sabatolimab will be administered on

Day 8 of the new cycle. In cases in which venetoclax and azacitidine have been permanently discontinued and the participant remains on sabatolimab, then, in participants who have achieved CR or mCR and have Grade 4 neutropenia and/or Grade 4 thrombocytopenia, dosing of sabatolimab should be interrupted until resolution to ≤ Grade 2. The first day dosing with sabatolimab is resumed will be considered D8 of the new cycle.

Dose modifications for sabatolimab

Dose modifications for sabatolimab will be done according to ASCO guidelines about management of immune-related AEs (Brahmer et al 2018).

Additionally, the guidance indicated in Table 6-5 below, provides instructions for infusion reaction, immune-related adverse events not covered by ASCO guidelines and a general guideline for non-hematologic non-immune-related toxicities that are clinically significant per investigator judgement and possibly attributable to the investigational drug. This general guideline will not apply in case of non-hematologic non-immune-related toxicities that are attributable to azacitidine, venetoclax and MDS and its complications.

Deviations to dose interruptions and/or permanent discontinuations outlined in Table 6-5 are not allowed.

Administration of sabatolimab may be delayed due to toxicities. A scheduled dose may be delayed within a cycle by up to 14 days. If a dose cannot be administered within the planned window within the cycle, then the dose should be skipped. Next scheduled dosing may resume once the adverse event has resolved to ≤ Grade 1 or baseline per the next planned treatment cycle. Dose reductions for sabatolimab are not allowed.

Overall, for adverse events of potential immune-related etiology (irAE) that do not recover to ≤ Grade 1 or baseline at a dose of immunosuppression of ≤ 10 mg/day prednisone or equivalent (or as indicated in Table 6-5) within 12 weeks after initiation of immunosuppressive therapy, sabatolimab must be permanently discontinued.

Table 6-5 Criteria for dose interruption and re-initiation or discontinuations of sabatolimab for adverse drug reactions

Worst Toxicity Grade (CTCAE v5.0)	Recommended Dose Modifications
Infusion Reaction	
Grade 1	Decrease infusion rate until recovery
Grade 2	Stop infusion Before restarting – pre-medicate according to local institutional guidelines. Restart infusion at 50% of previous rate under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion(s).If the AE recurs at the reinitiated slow rate of infusion, and despite oral pre-medication*, then discontinue sabatolimab
Grade 3	Stop infusion If the AE resolves to ≤ Grade 1 within 72hrs:

Worst Toxicity Grade (CTCAE v5.0)	Recommended Dose Modifications
	· At next scheduled treatment visit, pre-medicate according to local institutional guidelines. · Restart infusion at 50% of previous rate under continuous observation. Ensure that there is a minimum observation period of 1 hour. · If the AE recurs despite slow rate of infusion and pre-medication*, then discontinue sabatolimab. If the AE does not resolve to ≤ Grade 1 within 72hrs: · Discontinue sabatolimab
Grade 4	Discontinue sabatolimab

For adverse events thought to be immune-related AEs and not covered in the ASCO Guidelines for the management of immune-related adverse events in participants treated with immune checkpoint inhibitor therapy (Brahmer et al 2018**)**

Grade 1	Continue treatment with sabatolimab
Grade 2 or Grade 3 ≤ 7 days	Delay treatment with sabatolimab until resolved to ≤ Grade 1 or baseline
Grade 3 lasting > 7 days but < 21 days	1st and 2nd occurrence Delay study treatment until resolved to ≤ Grade 1 or baseline 3rd occurrence: Discontinue study treatment
Grade 3 lasting ≥ 21 days Or Grade 4	Discontinue study treatment
Dermatological toxicities	
Grade 1	Maintain sabatolimab. Use topical steroids, antihistamines, topical emollients.
Grade 2	Consider interrupting sabatolimab. Use topical or oral steroids, antihistamines. If sabatolimab is interrupted and resolution to ≤ Grade 1, restart sabatolimab.
Grade 3 or 4	Interrupt sabatolimab. Manage per institutional practice. After resolution to ≤ Grade 1, consider restarting sabatolimab.
Bullous dermatitis	Grade 1, 2 and 3: Interrupt sabatolimab. Consult with dermatologist for appropriateness to restart sabatolimab. Grade 4: Permanently discontinue sabatolimab.
Stevens-Johnson syndrome (SJS), or Lyell syndrome/toxic epidermal necrolysis (TEN)	Permanently discontinue sabatolimab.
For non-hematological, non immune related toxicities clinically significant and at least possible attributable to sabatolimab (NCI CTCAE v5.0)** *(The guideline does not apply to for toxicities attributable to azacitidine or venetoclax or the underlying MDS including its complications)*	

[redacted]

Worst Toxicity Grade (CTCAE v5.0)	Recommended Dose Modifications
Grade 1 and Grade 2 tolerable	Continue treatment with sabatolimab
Grade 2 intolerable (includes all Grade 2 events defined as DLT in Table 6 4) and Grade 3	1st or 2nd occurrence: · Interrupt sabatolimab until toxicity recovers to ≤ Grade 1 or baseline · Once recovered to ≤ Grade 1 or baseline restart sabatolimab at the same dose level and schedule AE resolution to ≤ Grade 1 or baseline must occur within a maximum period of 56 days since interruption, otherwise sabatolimab must be permanently discontinued. 3rd occurrence: · Permanently discontinue sabatolimab
Grade 4	Discontinue sabatolimab

All dose modifications should be based on the available information and worst preceding toxicity
*Prophylaxis regimens will include both paracetamol/acetaminophen and an antihistamine. **Per investigator judgement

Dose modifications for azacitidine

If azacitidine treatment is deemed by the investigator to possibly have contributed to an observed adverse event, the dose or schedule of azacitidine treatment may be modified within a cycle and/or for subsequent cycles or temporary/permanent interruptions of azacitidine treatment may be decided by the investigator according to local practice and/or the country-specific label guiding azacitidine use.

Dose modifications for venetoclax

If venetoclax treatment is deemed by the investigator to possibly have contributed to an observed adverse event, the dose or duration of venetoclax treatment may be modified according to the following guidelines:

Table 6-6 Dose modifications for venetoclax

Event	Occurrence	Action
Grade 4 neutropenia with or without fever or infection; or Grade 4 thrombocytopenia	Occurrence prior to achieving remission	Transfuse blood products, administer prophylactic and treatment anti-infectives as clinically indicated.
	First occurrence after achieving remission and lasting at least 7 days	Delay subsequent treatment and monitor blood counts. Administer granulocyte-colony stimulating factor (G-CSF) if clinically indicated for neutropenia.

Event	Occurrence	Action
		Once the toxicity has resolved to Grade 1 or 2, resume venetoclax therapy at the same dose.
	Subsequent occurrences in cycles after achieving remission and lasting at least 7 days	Delay subsequent treatment and monitor blood counts. Administer G-CSF if clinically indicated for neutropenia. Once the toxicity has resolved to Grade 1 or 2, resume venetoclax therapy at the same dose and the duration reduced by 7 days for each subsequent cycle.
Blood chemistry changes suggestive of TLS	-	Withhold treatment. If the event is resolved within 48 hours of last dose, treatment with venetoclax can be resumed at the same dose.
Events of clinical TLS or blood chemistry changes requiring more than 48 hours to resolve	-	Withhold treatment. Treatment should be resumed at a reduced dose (per the investigator discretion). When resuming treatment after interruption due to TLS, the instructions for prevention of TLS should be followed.
Grade 3 or 4 non-hematologic toxicities	First occurrence	Withhold treatment. Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose.
	Subsequent occurrences	Withhold treatment. Treatment should be resumed at a reduced dose (per the investigator discretion).

Permanent discontinuation of study treatment

If the study treatment (i.e. sabatolimab + azacitidine + venetoclax) is interrupted for toxicities and the start of the subsequent study treatment cycle is delayed for more than 28 consecutive days (measured from the intended start date of the new cycle (Day 29 of the previous cycle), the participant should be discontinued from study treatment.

At any time during the study, participants unable to tolerate one or two of the study treatment drugs may continue study treatment with only the tolerated drug(s) provided the participant benefits per investigator's judgement.

These dose changes must be recorded on the appropriate CRF.

[redacted]

6.5.4 Follow-up for toxicities

Participants whose treatment is interrupted or permanently discontinued due to an AE or clinically significant laboratory value, must be followed-up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary.

All participants must be followed up for AEs (including irAEs and SAEs) for 30 days following the last dose of venetoclax or azacitidine (whichever was later) and 150 days following the last dose of sabatolimab, whichever is later.

6.5.4.1 Follow-up for immune-related AEs

The emergence of Immune-Related AE (irAE) may be anticipated based on general experience in clinical studies with similar class of compounds that block the negative immune regulators.

An irAE is any clinically significant AE affecting any organ that is associated with study drug exposure, is consistent with an immune-mediated mechanism, and where alternative explanations have been investigated and ruled out or are considered to be unlikely. Serologic, histologic and immunological assessments should be performed as deemed appropriate by the Investigator, to verify the immune related nature of the AE. An empiric trial of corticosteroids may also contribute to understanding the etiology of a potential irAE. All participants with signs or symptoms of irAEs should be monitored and managed following the ASCO Guidelines for the management of immune-related adverse events in participants treated with immune checkpoint inhibitor therapy (Brahmer et al 2018). See guidance in Table 6-5 for immune-related AEs not covered by ASCO guidelines.

In case of a suspected irAE, the relevant immunological assessments (e.g. rheumatoid factor, anti-DNA Ab, etc.) should be performed. In case of a toxicity suspected to be a cytokine release syndrome, the cytokine assessments outlined in Table 8-1 must be performed.

Participants should be monitored carefully for any skin toxicity or mucositis and study treatment should be discontinued for any suspected case of SJS/TEN.

6.5.4.2 Follow-up for Tumor Lysis Syndrome (TLS)

Tumor lysis syndrome (TLS) is a clinical entity observed in some hematological malignancies resulting from massive tumor cells lysis. It is characterized by a constellation of metabolic abnormalities caused by the massive and abrupt release of cellular components (including nucleic acids, proteins, and electrolytes) into the systemic circulation after the rapid lysis of malignant cells (Cairo and Bishop 2004, Coiffier et al 2008).

TLS is not frequent in MDS and no cases of TLS have been reported in the ongoing [CPDR001X2105] for participants receiving sabatolimab in combination with hypomethylating agents.

Futhermore no cases of clinical TLS have been reported when MDS participants were treated with venetoclax in combination with azacitidine (Wei et al 2019, Ball et al 2020, Azizi et al 2020).

Nevertheless, during this study, participants should be closely monitored (including relevant laboratory tests) for signs and symptoms of TLS before initiation and during a treatment cycle. At Cycle 1, all participants involved in the Safety run-in (Part 1) must be hospitalized from Day 1 to Day 3 [clinical signs and chemistry will be monitored daily] and thereafter at the investigator's discretion.

To minimize risk of TLS, all participants should receive allopurinol, or an alternative prophylaxis with anti-hyperuricemic agents, as well as adequate hydration (including instructing participants to drink 1.5 to 2.0 L of water daily, among other measures as clinically indicated), prior to study treatment. Events should be managed according to local guidelines.

Before initiation of a treatment cycle and during a treatment cycle, the following measures should be followed:

Before initiation of a treatment cycle

· Prophylactic allopurinol, or a non-allopurinol alternative (eg, febuxostat), and increased oral/ i.v. hydration prior to treatment should be given in participants with elevated uric acid or high tumor burden

· Prompt supportive care in case of acute TLS (i.v. fluids and treatment with rasburicase as clinically indicated, when uric acid continues to rise despite allopurinol/febuxostat and fluids)

During a treatment cycle

· Frequent monitoring of the following laboratory tests (per assessment cycle and as clinically indicated): potassium, phosphorus, calcium, creatinine, and uric acid

· Encourage oral hydration

Based on laboratory and clinical TLS criteria (modified from Cairo and Bishop 2004), the following measures for TLS should be also followed:

Laboratory tumor lysis syndrome

· Defined as two or more of the following values within three days before or in the days following initiation of a treatment cycle:

· Uric acid ≥ 8 mg/dL or 25% increase from baseline

· Potassium ≥ 6 mEq/L or 25% increase from baseline

· Phosphorus ≥ 6.5 mg/dL (children) or ≥ 4.5 mg/dL (adults) or 25% increase from baseline

· Calcium ≤ 7 mg/dL or 25% decrease from baseline

· Regimen:

· If none or one of the laboratory values above is abnormal, continue to manage with allopurinol or a non-allopurinol alternative (e.g., febuxostat) and oral fluids. If uric acid remains elevated, consider i.v. fluids, treatment with rasburicase, and hospital monitoring.

· Laboratory TLS should be managed with i.v. fluids, laboratory blood tests every 6 to 8 hours and inparticipant care. Cardiac monitoring and treatment with rasburicase should be considered if uric acid remains elevated.

Clinical tumor lysis syndrome

· Defined as the presence of laboratory TLS and ≥ 1 of the following criteria that cannot be explained by other causes:

· Serum creatinine ≥ 1.5 times the upper limit of the age-adjusted normal range

· Symptomatic hypocalcemia

· Cardiac arrhythmia

· Regimen:

· Clinical TLS should be managed with i.v. fluids, laboratory blood tests every 6 to 8 hours, cardiac monitoring, treatment with rasburicase/allopurinol/febuxostat and inparticipant care (consider intensive care unit (ICU)).

Participants who have been treated for TLS with favorable outcome (defined as return to within 10% of baseline value or within limit of normal of relevant laboratory parameters) may re-start study treatment upon investigator's discretion.

6.5.4.3 Follow up on potential drug-induced liver injury (DILI) cases

Guidelines for follow-up on potential DILI cases are described in Table 6-7 and Table 6-8.

Table 6-7 Follow-up of abnormal liver chemistry results

ALT	TBL	Liver Symptoms	Action
ALT increase without bilirubin increase:			
If normal at baseline: ALT > 3 x ULN	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	- No change to study treatment - Measure ALT, AST, ALP, GGT, TBL, INR, albumin, CK, and GLDH in 48-72 hours. - Follow-up for symptoms
If elevated at baseline: ALT > 2 x baseline or > 200 U/L (whichever occurs first)			
If normal at baseline: ALT > 5 x ULN for more than two weeks	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	- Interrupt study drug - Measure ALT, AST, ALP, GGT, TBL, INR, albumin,
If elevated at baseline:			

ALT	TBL	Liver Symptoms	Action
ALT > 3 x baseline or > 300 U/L (whichever occurs first) for more than two weeks			CK, and GLDH in 48-72 hours. - Follow-up for symptoms. - Initiate close monitoring and workup for competing etiologies. - Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
If normal at baseline: ALT > 8 x ULN	Normal	None	
ALT increase with bilirubin increase:			
If normal at baseline: ALT > 3 x ULN	TBL > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
If elevated at baseline: ALT > 2 x baseline or > 200 U/L (whichever occurs first)			
If normal at baseline: ALT > 3 x ULN	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	
If elevated at baseline: ALT > 2 x baseline or > 200 U/L (whichever occurs first)			

Table 6-8 Action required for isolated total bilirubin elevation

Abnormality	Action required
Any elevation > ULN	Fractionate bilirubin, evaluate for cholestatic liver injury (ALP) or alternative causes of bilirubin elevation. Treat alternative causes according to local institutional guidelines
Grade 2 (>1.5 - 3.0 ULN)	Maintain treatment. Repeat LFTs within 48-72 hours, then monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline

Abnormality	**Action required**
Grade 3 (>3.0 – 10 ULN)	Interrupt treatment. Repeat LFTs within 48-72 hours, then monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline
Grade 4 (> 10 x ULN)	Discontinue study treatment

If abnormalities are confirmed, close observation and follow-up are required:

1. A detailed history, including relevant information, such as cardiac disease, history of any pre-existing liver conditions or risk factors, blood transfusions, i.v. drug abuse, travel, work, alcohol intake, and full clinical examination for evidence of acute or chronic liver disease, cardiac disease and infection etc. should be performed.

2. Review of concomitant medications, including nonprescription medications and herbal and dietary supplement preparations, alcohol use, recreational drug use, special diets, and chemicals exposed to within one month of the onset of the liver injury.

3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.

4. Obtain an unscheduled PK sample, as close as possible to last dose of study treatment.

Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

6.5.4.4 Follow-up for QTcF Prolongation

In case of QTcF >480 ms (or QTcF prolongation >60 ms from baseline):

· Assess the quality of the ECG recording. Collect two additional ECGs as soon as possible and submit the triplicate for central review.

· Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities.

· Review concomitant medication use for possible causes for QT prolongation (refer to crediblemedicines.org). Record all concomitant medications in the appropriate eCRF page.

· Monitor ECG per the institutional standards.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Every time study treatment sabatolimab is to be administered, IRT must be contacted to assign a medication (kit) number and (where applicable) for registration of the other study drugs dispensed to the participants.

For study treatment taken at home (e.g. for tablets of venetoclax), 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.

The date and time of all study treatment administrations (sabatolimab, venetoclax, and azacitidine) during the study and any deviations from the protocol treatment schedule will be captured by the investigator staff on the appropriate study treatment dispensing form. Compliance with the study treatment and any protocol deviations will be assessed by the field monitor on an ongoing basis. All study treatment dispensed and returned (if applicable) must be recorded in the Drug Accountability Log.

Pharmacokinetic parameters (measures of sabatolimab and venetoclax) will be determined in all participants treated with sabatolimab, as detailed in the pharmacokinetic section (Section 8.5.2).

6.6.2 Emergency breaking of assigned treatment code

Not applicable.

6.7 Preparation and dispensation

The investigator or responsible site personnel must instruct the participant or caregiver to take the study treatment as per protocol. Study drug(s) will be dispensed to the participant by authorized site personnel only.

All dosages for study treatment (sabatolimab, azacitidine and venetoclax) prescribed to the participant and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

Sabatolimab

Each study site will be supplied by Novartis with the investigational drug sabatolimab as global clinical open supply and will be packed and labeled under the responsibility of Novartis.

Investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

Sabatolimab will be administered i.v. Further instructions for the preparation and dispensation of sabatolimab are described in the Pharmacy Manual.

Azacitidine

Azacitidine may be administered i.v or subcutaneously. Use of oral azacitidine is not allowed.

For details on preparation refer to the country-specific label instructions and/or azacitidine package insert.

Venetoclax

[redacted]

Participants will be provided with adequate supply of venetoclax (tablets for oral administration) for on-site administration, if applicable, or for self-administration at home, including instructions for administration, until at least their next scheduled study visit. Venetoclax will be supplied globally or locally.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 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 and in the Investigator's Brochure. 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 monitors during site visits or remotely and at the completion of the trial. 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.

At the conclusion of the study, and as appropriate during the course of the study, 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.

The study drug supply can be destroyed at the local Novartis facility or third party, as appropriate, or locally at site only if permitted by local regulations and authorized by Novartis.

6.7.1.2 Handling of additional treatment

Not applicable.

6.7.2 Instruction for prescribing and taking study treatment

Please refer to Section 6.1.1.

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.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent

possible given his/her understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

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 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 drug 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 subjects or the female partners of any male subjects who took study treatment

Women of childbearing 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 for the duration of the study. If there is any question that the participant will not reliably comply, they should not be entered in the study.

Male participants, including vasectomized men, in the study, must agree not to father a child and to use a condom during intercourse, to prevent delivery of the drug via seminal fluid during the study, and for the period of 3 months after the last dose of azacitidine.

Prior to starting treatment, male participants are advised to seek consultation on sperm storage and female participants of childbearing potential should seek consultation regarding oocyte cryopreservation.

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

[redacted]

8 Visit schedule and assessments

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

Each treatment cycle is 28 days. Screening evaluations should be performed within ≤ 28 days of Cycle 1 Day 1 (except for the pregnancy test which has to be performed within 72 hours before the first dose).

During the course of the study visits, test and/or procedures should occur on schedule whenever possible. A visit window of +/- 3 days is allowed for study procedures (including treatment administration). If sabatolimab administration on Day 8 is delayed within a cycle due to toxicities, visit assessments for Day 8 should be shifted accordingly or occur on Day 22, in case of no administration. See Section 6.1 for details on study treatment.

A window of+/- 7 days from the planned visit date is allowed for BMA procedures. During the post-treatment and survival follow-up phases, a visit window of +/- 14 days is allowed.

Note: If a treatment cycle is delayed at any time during the study, all study visits and safety and efficacy assessments should continue according to the appropriate number of calendar days measured from Day 1 of the previous cycle, or more often if clinically indicated. When treatment is resumed, the first day of azacitidine and venetoclax administration will be considered as D1 of the new treatment cycle and visit schedule will be shifted accordingly.

On PK collection days the windows are provided in Section 8.5.2. Participants who discontinue the study treatment for any reason should be scheduled for an end of treatment (EOT) visit within 14 days from the decision to permanently discontinue study treatment, at which time all of the assessments listed for the EOT visit will be performed.

For efficacy follow-up and survival information, please refer to Section 8.3.1 and Section 9.1.

[redacted]

Table 8-1 Assessment Schedule

Period	Screening	Treatment																		
Cycle		Cycle 1				Cycle 2				Cycle 3			Cycle 4			Cycle 5			Cycle 6	
Visit Name	Screening (-28 to -1)	D1	D8	D22	D28	D1	D8	D22	D28	D1	D8	D28	D1	D8	D28	D1	D8	D28	D1	D8
Days	-28 to -1	D1	D8	D22	D28	D1	D8	D22	D28	D1	D8	D28	D1	D8	D28	D1	D8	D28	D1	D8
Informed consent	X																			
IRT Registration	X	X																		
Demography	X																			
Inclusion / Exclusion criteria	X																			
Medical history/current medical conditions	X																			
Disease History[1]	X																			
Prior antineoplastic therapies	X																			
Prior/concomitant medications, surgery and medical procedures (including blood transfusions requirement)[2]	X																			
Adverse Events	X	Continuous																		
Physical Examination	S	S	S	S		S	S	S		S	S		S	S		S	S		S	S
Vital Signs	X	X	X	X		X	X	X		X	X		X	X		X	X		X	X
Body Height	X																			
BSA (use height from screening)		X				X				X			X			X			X	
Body Weight	X	X				X				X			X			X			X	
ECOG PS	X	X				X				X			X			X			X	
Hematology	X	X	X	X		X	X	X		X	X		X	X		X	X		X	X

[redacted]

Period	**Screening**	**Treatment**																		
Cycle		**Cycle 1**				**Cycle 2**				**Cycle 3**			**Cycle 4**			**Cycle 5**			**Cycle 6**	
Visit Name	**Screening (-28 to -1)**	**D1**	**D8**	**D22**	**D28**	**D1**	**D8**	**D22**	**D28**	**D1**	**D8**	**D28**	**D1**	**D8**	**D28**	**D1**	**D8**	**D28**	**D1**	**D8**
Days	**-28 to -1**	**D1**	**D8**	**D22**	**D28**	**D1**	**D8**	**D22**	**D28**	**D1**	**D8**	**D28**	**D1**	**D8**	**D28**	**D1**	**D8**	**D28**	**D1**	**D8**
Chemistry	X[3]	Pre-dose and at 7 hrs (+_1hr) post dose during first cycle from Day 1 to Day 3, then at Predose on Day 1 of every subsequent Cycle, at EOT and unscheduled as clinically indicated																		
Coagulation	X	X				X				X			X			X			X	
Cytogenetics [4]	X																			
Ferritin, iron, erythrocyte and serum folates, vitamin B12	X	If clinically indicated																		
Cytokines for safety	X	Anytime for a suspected cytokine release syndrome, immediately after the AE, and one week after occurrence of AE																		
Urinalysis (dipstick)	S	If clinically indicated																		
Thyroid function[5]	X					X										X				
Virology hepatitis B and C	S	If clinically indicated																		
HIV serology (only if required per local regulation)	S																			
Additional hepatic tests in case of DILI[6]	X[7]	If clinically indicated																		
Serum Pregnancy test [8]	S	S[9]																		
Urine Pregnancy Test OR Serum Pregnancy Test[8]						S				S			S			S			S	
12-Lead ECG (triplicates)[10]	X	X	X			S				S	X		S			S			S	
IRT - Drug dispensation for sabatolimab			X				X				X			X			X			X

[redacted]

Period	**Screening**	**Treatment**																		
Cycle		**Cycle 1**				**Cycle 2**				**Cycle 3**			**Cycle 4**			**Cycle 5**			**Cycle 6**	
Visit Name	**Screening (-28 to -1)**	**D1**	**D8**	**D22**	**D28**	**D1**	**D8**	**D22**	**D28**	**D1**	**D8**	**D28**	**D1**	**D8**	**D28**	**D1**	**D8**	**D28**	**D1**	**D8**
Days	**-28 to -1**	**D1**	**D8**	**D22**	**D28**	**D1**	**D8**	**D22**	**D28**	**D1**	**D8**	**D28**	**D1**	**D8**	**D28**	**D1**	**D8**	**D28**	**D1**	**D8**
IRT - Drug dispensation for venetoclax and azacitidine[11]		X				X				X			X			X			X	
Sabatolimab infusion			X				X				X			X			X			X
Venetoclax administration		400 mg daily po D1 to D14 of each cycle																		
Azacitidine infusion		on Days 1- 7 of each Cycle OR on Days 1-5 and then on Day 8 and Day 9 of each cycle																		
Efficacy - Bone marrow aspirate and/or biopsy AND peripheral blood smears	X									X										
Efficacy - response assessment[12]										X										
Efficacy - Peripheral blood collection	X									X										
PK sampling for sabatolimab[13]			X				X				X									X
PK sampling for venetoclax[14]			X								X									
Immunogenicity (IG) sampling for sabatolimab[13]			X				X				X									X
[redacted]																				

Period	**Screening**	**Treatment**																			
Cycle		**Cycle 1**				**Cycle 2**				**Cycle 3**			**Cycle 4**			**Cycle 5**			**Cycle 6**	
Visit Name	**Screening (-28 to -1)**	**D1**	**D8**	**D22**	**D28**	**D1**	**D8**	**D22**	**D28**	**D1**	**D8**	**D28**	**D1**	**D8**	**D28**	**D1**	**D8**	**D28**	**D1**	**D8**
Days	**-28 to -1**	**D1**	**D8**	**D22**	**D28**	**D1**	**D8**	**D22**	**D28**	**D1**	**D8**	**D28**	**D1**	**D8**	**D28**	**D1**	**D8**	**D28**	**D1**	**D8**
[redacted]																				
Concomitant medications and medical procedures (including blood transfusions requirement)		Continuous																		
[redacted]																				
FACIT-Fatigue[17]		X			X				X			X						X		
[redacted]																				

[redacted]

Period	**Screening**	**Treatment**																		
Cycle		**Cycle 1**				**Cycle 2**				**Cycle 3**			**Cycle 4**			**Cycle 5**			**Cycle 6**	
Visit Name	**Screening (-28 to -1)**	**D1**	**D8**	**D22**	**D28**	**D1**	**D8**	**D22**	**D28**	**D1**	**D8**	**D28**	**D1**	**D8**	**D28**	**D1**	**D8**	**D28**	**D1**	**D8**
Days	**-28 to -1**	**D1**	**D8**	**D22**	**D28**	**D1**	**D8**	**D22**	**D28**	**D1**	**D8**	**D28**	**D1**	**D8**	**D28**	**D1**	**D8**	**D28**	**D1**	**D8**
Hospitalizations[20]		X																		
Antineoplastic therapies, HSCT and transfusions since discontinuation of study treatment																				
Disposition	X																			
Survival Follow-up																				

Period	**Treatment**				**End of Treatment**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**
Cycle	**Cycle 6**	**Cycle 7 (and subsequent cycles)**						
Visit Name	**D28**	**D1**	**D8**	**D28**	**EOT**	**30, 90, 150 day**	**Every 12 weeks until Disease Progression**	**Every 3 months**
Days	**D28**	**D1**	**D8**	**D28**	**EOT**	**30, 90, 150 days**	**Every 12 weeks**	**Every 12 weeks**
Informed consent								
IRT Registration					X			
Demography								
Inclusion / Exclusion criteria								
Medical history/current medical conditions								
Disease History[1]								
Prior antineoplastic therapies								

[redacted]

Period	**Treatment**				**End of Treatment**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**
Cycle	**Cycle 6**	**Cycle 7 (and subsequent cycles)**						
Visit Name	**D28**	**D1**	**D8**	**D28**	**EOT**	**30, 90, 150 day**	**Every 12 weeks until Disease Progression**	**Every 3 months**
Days	**D28**	**D1**	**D8**	**D28**	**EOT**	**30, 90, 150 days**	**Every 12 weeks**	**Every 12 weeks**
Prior/concomitant medications, surgery and medical procedures (including blood transfusions requirement)[2]								
Adverse Events	Continuous					X[21]		
Physical Examination		S	S		S			
Vital Signs		X	X		X			
Body Height								
BSA (use height from screening)		X						
Body Weight		X			X			
ECOG PS		X			X			
Hematology		X	X		X		every 12 weeks (aligned to time of response assessments) and if clinically indicated[22]	
Chemistry	Pre-dose and at 7 hrs (+_1hr) post dose during first cycle from Day 1 to Day 3, then at Predose on Day 1 of every subsequent Cycle, at EOT and unscheduled as clinically indicated							
Coagulation		X			X			
Cytogenetics [4]								

[redacted]

Period	**Treatment**				**End of Treatment**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**
Cycle	**Cycle 6**	**Cycle 7 (and subsequent cycles)**						
Visit Name	**D28**	**D1**	**D8**	**D28**	**EOT**	**30, 90, 150 day**	**Every 12 weeks until Disease Progression**	**Every 3 months**
Days	**D28**	**D1**	**D8**	**D28**	**EOT**	**30, 90, 150 days**	**Every 12 weeks**	**Every 12 weeks**
Ferritin, iron, erythrocyte and serum folates, vitamin B12	If clinically indicated							
Cytokines for safety	Anytime for a suspected cytokine release syndrome, immediately after the AE, and one week after occurrence of AE							
Urinalysis (dipstick)	If clinically indicated							
Thyroid function[5]		at Cycle 8 Day 1 then every 3 cycles (Day 1) thereafter and as clinically indicated			X			
Virology hepatitis B and C	If clinically indicated							
HIV serology (only if required per local regulation)								
Additional hepatic tests in case of DILI[6]	If clinically indicated							
Serum Pregnancy test [8]					S			
Urine Pregnancy Test OR Serum Pregnancy Test[8]		S				monthly[23]		
12-Lead ECG (triplicates)[10]		S			X			
IRT - Drug dispensation for sabatolimab			X					

[redacted]

Period	**Treatment**				**End of Treatment**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**
Cycle	**Cycle 6**	**Cycle 7 (and subsequent cycles)**						
Visit Name	**D28**	**D1**	**D8**	**D28**	**EOT**	**30, 90, 150 day**	**Every 12 weeks until Disease Progression**	**Every 3 months**
Days	**D28**	**D1**	**D8**	**D28**	**EOT**	**30, 90, 150 days**	**Every 12 weeks**	**Every 12 weeks**
IRT - Drug dispensation for venetoclax and azacitidine[11]		X						
Sabatolimab infusion			X					
Venetoclax administration	400 mg daily po D1 to D14 of each cycle							
Azacitidine infusion	on Days 1- 7 of each Cycle OR on Days 1-5 and then on Day 8 and Day 9 of each cycle							
Efficacy - Bone marrow aspirate and/or biopsy AND peripheral blood smears		At Cycle 7 Day 1, Cycle 10 Day 1, Cycle 13 Day 1, then every 6 cycles (C19D1 and C25D1), then every 12 cycles (C37 Day 1, C49D1, etc.) and when clinically indicated at any time during the treatment period. At EOT and thereafter at least every 12 months and anytime if clinically indicated during the efficacy follow-up period						
Efficacy - response assessment[12]		At Cycle 7 Day 1, Cycle 10 Day 1, Cycle 13 Day 1, then every 6 cycles (C19D1 and C25D1), then every 12 cycles (C37 Day 1, C49D1, etc.) and when clinically indicated at any time during the treatment period. At EOT and thereafter at least every 12 months and anytime if clinically indicated during the efficacy follow-up period						
Efficacy - Peripheral blood collection		At Cycle 7 Day 1, Cycle 10 Day 1, Cycle 13 Day 1, then every 6 cycles (C19D1 and C25D1), then every 12 cycles (C37 Day 1, C49D1, etc.) and when clinically indicated at any time during the treatment period. At EOT and thereafter at least every 12 months and anytime if clinically indicated during the efficacy follow-up period						
PK sampling for sabatolimab[13]			At Day 8 of cycles 9, 12, 18 and 24		X	at 30 and 150 days (if visit is conducted at site)		
PK sampling for venetoclax[14]								

[redacted]

Period	**Treatment**				**End of Treatment**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**
Cycle	**Cycle 6**	**Cycle 7 (and subsequent cycles)**						
Visit Name	**D28**	**D1**	**D8**	**D28**	**EOT**	**30, 90, 150 day**	**Every 12 weeks until Disease Progression**	**Every 3 months**
Days	**D28**	**D1**	**D8**	**D28**	**EOT**	**30, 90, 150 days**	**Every 12 weeks**	**Every 12 weeks**
Immunogenicity (IG) sampling for sabatolimab[13]			At Day 8 of cycles 9, 12, 18 and 24		X	at 30 and 150 days (if visit is conducted at site)		
[redacted]								
Concomitant medications and medical procedures (including blood transfusions requirement)	Continuous						X[24]	
[redacted]								

[redacted]

Period	Treatment				End of Treatment	Safety Follow-up	Efficacy Follow-up	Survival Follow-up
Cycle	Cycle 6	Cycle 7 (and subsequent cycles)						
Visit Name	D28	D1	D8	D28	EOT	30, 90, 150 day	Every 12 weeks until Disease Progression	Every 3 months
Days	D28	D1	D8	D28	EOT	30, 90, 150 days	Every 12 weeks	Every 12 weeks
[redacted]								
FACIT-Fatigue[17]	X				X		Every 24 weeks (aligned with response assessment)[22]	
[redacted]								
Hospitalizations[20]								
Antineoplastic therapies, HSCT and transfusions since discontinuation of study treatment					Continuous			
Disposition					X		X	
Survival Follow-up								X

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 The last assessment of bone marrow and/or peripheral blood counts should be used within 28 days prior to enrollment.
2 Blood transfusions administered within 16 weeks prior to the first dose will be collected and recorded in the eCRF.
3 Blood chemistry should be confirmed within 72 hours prior to planned first dose.

[redacted]

Period	Treatment				End of Treatment	Safety Follow-up	Efficacy Follow-up	Survival Follow-up
Cycle	Cycle 6	Cycle 7 (and subsequent cycles)						
Visit Name	D28	D1	D8	D28	EOT	30, 90, 150 day	Every 12 weeks until Disease Progression	Every 3 months
Days	D28	D1	D8	D28	EOT	30, 90, 150 days	Every 12 weeks	Every 12 weeks

[4] Cytogenetics to be performed locally. Assessment to be recorded in the clinical database (eCRF)
[5] Any deficiency should be corrected before the start of Study Treatment. Refer to Table 8-3 for details on analytes to be tested.
[6] Refer to Section 6.5.4.3 for DILI follow-up
[7] Only GLDH to be tested at baseline - see Table 8-7
[8] This test will be performed only for women of child bearing potential
[9] Does not need to be performed if it was done in screening within 72 hours before first dose
[10] Refer to Section 8.4.2 for detailed guidance on timepoints
[11] Venetoclax will be dispensed via IRT on Day 1 of each Cycle. Azacitidine will be dispensed via IRT daily as per standard clinical practices.
[12] See Section 8.3.1 for details on response assessments
[13] See Table 8-9 for detailed PK/IG sampling timepoints and schedule
[14] See Table 8-10 for detailed timepoints and collection schedule for venetoclax PK sampling. Venetoclax PK sampling will be collected during Phase 1 (safety run-in) only.
[redacted]
[17] PROs will be collected during Phase 2 (expansion) only
[redacted]
[20] Hospitalization is required at Cycle 1 from Day 1 to Day 3 for subjects participating to the Safety run-in Part. Chemistry will be collected on pre-dose Day 1, Day 2 and Day 3 for TLS monitoring.
[21] If the patient begins new antineoplastic medication before the end of the safety follow-up period, then only suspected AEs and suspected SAEs will continue to be collected. See Section 10.1
[22] Starting from last on treatment efficacy assessment
[23] Pregnancy testing for women of child bearing potential should be performed monthly during the safety follow-up period (urine or serum test may be performed, depending on local regulations).
[24] Transfusions administered during efficacy follow-up will be recorded in the CRF every 12 weeks (aligned with efficacy assessment visits).

[redacted]

8.1 Screening

Screening

All participants must provide signed ICFs prior to performing any study specific procedures. Screening assessments to confirm eligibility should be performed as per the schedule of assessments detailed in Table 8-1. Participants will be evaluated against all study inclusion and exclusion criteria and safety assessments which must be completed within 28 days prior to the start of study treatment (C1D1), with the exception of the local serum pregnancy test (for women of childbearing potential) which must be conducted and confirmed as negative within 72 hrs prior to the start of study treatment. Laboratory parameters may be retested within the 28-day screening period. If the repeat value remains outside of the specified ranges, the participant will be considered a screen failure.

An individual participant may only be re-screened once for the study. A new ICF will need to be signed if the investigator chooses to re-screen the participant. Any re-screened participant should receive a new participant No., and the original participant number must be noted on the Re-Screening CRF. All required screening activities must be performed when the participant is re-screened for participation in the study.

8.1.1 Eligibility screening

Following registering in the IRT for screening, participant eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IRT system. Please refer and comply with detailed guidelines in the IRT manual.

8.1.2 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible prior to administration of study treatment (C1D1) will be considered a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form (CRF). 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 during the screening phase (see Section 10.1.3 for reporting details). If the participant is screen failed or will not be treated, the IRT is to be notified as soon as possible that the participant was not enrolled.

8.2 Participant demographics / other baseline characteristics

Demographics and other baseline characteristics data to be collected on all participants include:

- Disease history, including date of diagnosis, confirmation of MDS diagnosis, IPSS-R risk classification for MDS participants at time of screening, prior antineoplastic therapies. Calculation of IPSS-R risk score for MDS participants and should be done based on the hematology values obtained at screening.
- Relevant prior antineoplastic therapies and all concomitant medications and medical procedures

[redacted]

- Blood transfusions (RBC/platelets) **administered within 16 weeks** before the first dose is administered

Other assessments will be completed for the purpose of determining eligibility for inclusion in the study as reported in Table 8-1.

Assessments to be performed at screening include:

- After all study ICFs are signed the participant will be registered with the IRT
- Inclusion/exclusion criteria
- Medical history/current medical conditions
- Disposition
- Physical examination
- ECOG Performance Status, body height, weight, vital signs (blood pressure (supine position preferred when ECGs are collected) and pulse, and body temperature).
- Laboratory - hematology, blood chemistry, coagulation, urinalysis (dipstick and sediment), serum pregnancy test for women of child-bearing potential, thyroid function, cytogenetics, virology hepatitis B and C, HIV serology (only if required per local regulation)
- Triplicate 12-lead central ECG
- Bone marrow aspirate (BMA) or biopsy will be performed locally to establish the diagnosis. Cytogenetics will be performed locally as per local standard. If a bone marrow aspirate or biopsy was conducted during the regular work-up of the participant and fall within the 28 days prior to start of treatment (although prior to signing main study ICF), it may be considered as the baseline assessment for the study.

Bone marrow and peripheral blood pathology specimens (i.e. bone marrow slides, bone marrow biopsy block if applicable, peripheral blood smears) prepared locally for establishing the MDS diagnosis at the time of screening, should be sent to the Novartis designated central laboratory for storage. A copy of the corresponding pathology reports should be collected and sent to the Novartis designated central laboratory for storage. Central morphology review of the pathology specimens may be performed, if deemed necessary.

[redacted]

- Blood sample for Cytokines
- Adverse events

[redacted]

Authorities. Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature. Significant new findings that begin or worsen after informed consent must be recorded on the AE page of the participant's eCRF.

After all applicable study ICFs are signed, the participant will be registered in the IRT system.

8.3 Efficacy

8.3.1 Efficacy assessments

Disease response will be assessed locally by the investigator in all participants (MDS) according to modified IWG for MDS and WHO criteria (Cheson et al 2000, Cheson et al 2006, Arber et al, 2016, Platzbecker 2019). Response criteria are described in Table 8-2.

Investigators will assess and document response/progression at each time point as per the visit schedule. For efficacy analyses, baseline assessment is defined as the last non-missing assessment on or before the date of sabatolimab.

In addition, the hematological improvement per modified IWG-MDS criteria (Cheson et al 2006) will be assessed in all enrolled participants to report specific hematologic improvement (HI) of cytopenias in the three hematopoietic lineages: erythroid (HI-E), platelet (HI-P), and neutrophil (HI-N).

Table 8-2 Modified response classification per IWG-MDS criteria (Platzbecker et al 2019, Cheson et al 2006, Cheson et al 2000)

Response category	Definition[#]
Complete remission (CR)	**Bone marrow**: <= 5% blasts with normal maturation of all cell lineages. (Note: Persistence of dysplasia will be noted but does not preclude achievement of complete remission [CR]) **Peripheral blood**: 1. Hgb ≥ *10 g/dl* AND 2. Platelets ≥ $100*10^9$/L AND 3. Neutrophils ≥ $1.0*10^9$/L AND 4. Blasts 0% (Note: *the participant must not receive RBC or platelet transfusions, myeloid growth factor within 2 weeks before this disease assessment)*
marrow Complete remission (mCR)	**Bone marrow:**

Response category	Definition[#]
	<= 5% blasts and blast count decrease by ≥ 50% compared to baseline **Peripheral blood/transfusion:** Marrow CR may be achieved with or without improved blood counts or with or without transfusions
Partial remission (PR)	All CR criteria except **Bone marrow:** ≥ 50% decrease from baseline in blasts in bone marrow AND blast count in bone marrow > 5%
Stable Disease (SD)	Failure to achieve at least PR, but no evidence of progression for >8 weeks
Relapse from CR	**Only in participants with a CR** **At least 1 of the following criteria is met:** [in absence of another explanation not due to MDS, such as acute infection, bleeding, hemolysis, etc. Note that observation of peripheral blasts is not a sufficient criterion for relapse. However in that case, a bone marrow examination should be made to determine whether relapse has occurred] 1. Return to baseline bone marrow blast percentage 2. Decrease of ≥ 50% from maximum remission/response*** levels in neutrophils *AND neutrophils <1.0*10^9/L. Note: neutrophils counts during periods of active infection will not be considered in determining the maximum* 3. Decrease of ≥ 50% from maximum remission/response*** levels in platelets *AND platelets < 100*10^9/L* 4. Decrease *from maximum remission/response*** levels* in Hgb concentration by ≥ 1.5g/dL *AND Hgb < 10 g/dL* 5. Becoming transfusion dependent**
Disease progression	**At least 1 of the following criteria is met:**

Response category	Definition[#]
	[in absence of another explanation not due to MDS, such as acute infection, bleeding, hemolysis, etc. Note that observation of peripheral blasts is not a sufficient criterion for progression. However in that case, a bone marrow examination should be made to determine whether relapse has occurred] **Bone marrow** according to the number of blasts of the participant at baseline: 1. Less than 5% blasts *at baseline*: ≥ 50% increase in blasts *over baseline* to > 5% blasts 2. 5% - < 10% blasts *at baseline*: ≥ 50% increase *over baseline* to > 10% blasts 3. 10% - < 20% blasts *at baseline*: ≥ 50% increase *over baseline* to > 20% blasts. *Participants with more than 20% of blasts will be considered to have transformation to acute leukemia per 2016 WHO classification* (Arber et al, 2016) **Peripheral blood:** 1. Decrease of ≥ 50% from maximum remission/response*** levels in neutrophils *AND neutrophils < $1.0*10^9$/L. Note: neutrophils counts during periods of active infection will not be considered in determining the maximum* 2. Decrease of ≥ 50% from maximum remission/response*** levels in platelets *AND platelets < $100*10^9$/L* 3. Reduction *from maximum remission/response*** levels* in Hgb by ≥ 2g/dL *AND Hgb < 10g/dL* **Becoming transfusion dependent**** ***Occurrence of acute leukemia, or extramedullary leukemia per investigator's judgement***

Modified Hematologic Improvement per IWG-MDS criteria (Cheson et al 2006**)**

[redacted]

Response category	Definition[#]
HI category	**Definition[#] (HI must last at least 8 weeks)**
Erythroid response (HI-E) (pretreatment*, <11 g/dL)	1. Hgb increase from baseline by ≥ 1.5 g/dL, in at least 2 consecutive Hgb measurements and maintained over at least 8 weeks 2. Relevant reduction from baseline of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pre-treatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hgb of < 9 g/dL pre-treatment will count in the RBC transfusion response evaluation.
Platelet response (HI-P) (pretreatment*, <100 x 10^9/L)	1. Absolute increase from baseline of ≥ 30 x 10^9/L for participants starting with > 20 x 10^9/L platelets 2. Increase from baseline from < 20 x10^9/L to > 20 x10^9/L and by at least 100% for participants starting with < 20 x 10^9/L platelets
Neutrophil response (HI-N) (pretreatment*, <1.0 x 10^9/L)	At least 100% increase and an absolute increase from baseline of > 0.5 x 10^9/L

[#]If not defined otherwise, all of the criteria apply. Words that are written in italics highlights the modifications from the IWG criteria described in the reference publications.

**Pretreatment counts correspond to the baseline (not influenced by transfusions)*

**Definition of transfusion dependence and independence for red blood cells (RBC) and/or platelets are described below.

****maximum remission/response levels correspond to the best values reported in post baseline.*

Transfusions Status Definitions for RBC/platelets

Transfusions for intercurrent diseases not due to study indication (e.g. bleeding, surgical procedure, hemolysis, infections) should not be taken into account for the following:

Transfusion dependence:

1. At baseline: participants having received ≥ 3 units of transfusion within the 8 consecutive weeks prior to baseline.
2. Post-baseline: participants having received ≥ 3 units of transfusion within any 8 consecutive weeks during the course of the study

[redacted]

Transfusion independence:

1. At baseline: participants having received 0 units of transfusion within the 8 consecutive weeks prior to baseline.

2. Post-baseline: participants having received 0 units of transfusion within any 8 consecutive weeks during the course of the study.

Response assessment will be performed by investigator according to the assessment schedule depicted in Table 8-1. Moreover, participants can be assessed for disease response (bone marrow assessment, hematology, transfusion) at any time if clinically indicated as an example if there is a clinical suspicion of progression/relapse, in particular after a participant has achieved a CR.

Bone marrow assessments will be performed at screening and pre-dose on C3D1. From C7D1, bone marrow assessments will be performed every 3 cycles until C13D1 (C7D1, C10D1, C13D1), then every 6 cycles until C25D1 (C19D1 and C25D1) and thereafter every 12 cycles (C37D1, C49D1 etc.) and as clinically indicated during the treatment period.

Hematology assessments will be performed at screening, pre-dose on D1, D8 and D22 of Cycles 1 and 2, and thereafter pre-dose on D1 and D8 of each cycle until end of treatment.

Bone marrow and peripheral blood pathology specimens (i.e. bone marrow aspirate slides, bone marrow biopsy block if applicable, peripheral blood smears) prepared locally for the disease response assessment, should be sent to the Novartis designated central laboratory for storage. This includes specimens taken during the regular work-up of the participant and used as baseline assessment for the study as mentioned in Section 8.2 . A copy of the corresponding pathology reports should be collected and sent to the Novartis designated central laboratory for storage. Central morphology review of the pathology specimens may be performed, if deemed necessary. For China only: Storage of the above pathology specimens and reports in a Novartis designated laboratory will be performed, if adequate approval has been obtained from all relevant Chinese authorities.

Participants who discontinue treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent, will enter the efficacy follow-up phase.

In the efficacy follow-up phase, hematology assessments must continue to be performed every 3 months, response should be assessed at least every 12 months, and bone marrow assessment should be done at least every 12 months thereafter per Table 8-1, or as clinically indicated any time in case disease progression is suspected. Further information about blood transfusions will be continuously collected throughout the efficacy follow-up period.

The efficacy follow-up period will last until participant's documented disease progression (per IWG criteria Table 8-2), death, lost to follow-up, or withdrawal of consent, or the end of the study whichever comes first. Post-treatment antineoplastic therapies, including HSCT, will continue to be captured during survival follow-up (see Section 9.1.1.3 and Table 8-1).

8.3.2 Appropriateness of efficacy assessments

The assessment of response to study treatment is based on standardized criteria as proposed by modified IWG-MDS criteria (Cheson et al 2006) in Table 8-2.

[redacted]

8.4 Safety

Safety assessments are specified in Table 8-3 below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section.

Table 8-3 Assessments and specifications

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 complete physical examination is required at D1 of each cycle. At D8 of each cycle and D22 of Cycles 1 and 2, an abbreviated examination can be done at investigator's discretion. 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 CRF 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 include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature.
Height and weight	Height in centimeters (cm) will be measured at Screening. Body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured at screening and at subsequent timepoints as specified in Table 8-1

[redacted]

Performance status:

ECOG Performance status scale will be used as described in Table 8-4.

Table 8-4 ECOG performance status

Grade	ECOG Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Death

8.4.1 Laboratory evaluations

Local clinical laboratory parameters will be used for the analysis of scheduled hematology, chemistry and other blood specimens collected as part of safety monitoring (as detailed in Table 8-1 and Table 8-5) and the results will be collected in the eCRF.

Unscheduled assessments of these parameters can be performed more often as clinically indicated. It is preferable to use the same laboratory for all the assessments performed, especially for the hematology assessments.

A central laboratory will be used for the parameters listed in Table 8-6 and as per the schedule in Table 8-1.

Laboratory values obtained during the Screening phase will be used to assess participant's eligibility.

Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for all local laboratories used in the trial.

Table 8-5 Local clinical laboratory parameters collection plan

Test Category	**Test Name**
Hematology	Hemoglobin (Hgb), white blood cells (WBC), differential (including basophils, eosinophils, lymphocytes, monocytes, neutrophils, bands, metamyelocytes, myelocytes, promyelocytes, blasts), atypical cells (e.g. LUC, erythroblasts), platelets

[redacted]

Test Category	**Test Name**
	(absolute value preferred, %s are acceptable)
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphorus, Sodium, Potassium, Bicarbonate, Creatinine, Creatine kinase, Total Bilirubin, (Indirect Bilirubin, Direct Bilirubin)*, Total Cholesterol, Total Protein, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (fasting), Troponin-T or Troponin-I, NTproBNP**
Virology***	HBsAg, HBcAb, HBV DNA (in participants positive for HBcAb), HCV RNA (PCR) HIV (Only if required by local regulation)
Coagulation	International normalized ratio [INR]), Activated partial thromboplastin time (APTT)
Thyroid	At baseline: TSH, Free-T3 and Free-T4. During treatment: TSH at timepoints indicated in Table 8-1 and as clinically indicated. If TSH is abnormal, then test free-T3 and free-T4.
Urinalysis*** (dipstick)	Dipstick examination includes specific gravity, pH, glucose, protein, blood, bilirubin, ketones and WBC as clinically indicated. If urinalysis dipstick shows abnormalities, the site should perform a more detailed urinalysis follow-up as clinically indicated and per local practice.
Pregnancy Test***	Serum / Urine pregnancy test (refer to Section 8.4.3 'Pregnancy and assessments of fertility')
Additional Tests	Ferritin, iron, vitamin B12, erythrocyte and/or serum folates ****

* Indirect and direct bilirubin only required if total bilirubin is abnormal
** NTproBNP may be required as an additional test upon signs/symptoms and based on cardiology consult

[redacted]

*** Virology, urinalysis, and pregnancy test will only be reported in the source documentation
**** Preferred method is erythrocyte folate but in case is not available then serum should be performed. However, every effort should be made to perform both test.

Table 8-6 Central clinical laboratory parameters collection plan

Test category	Test Name
Cytokines	IFN-γ, IL-6, IL-1b, TNF-α
Chemistry for DILI [1]	Glutamate dehydrogenase (GLDH)

[1] at baseline and as clinically indicated for follow-up of DILI per Section 6.5.4.3

8.4.2 Electrocardiogram (ECG)

The ECGs are to be collected with ECG machines supplied by the central laboratory during the following timepoints: Screening, C1D1 predose, C1D8 post dose, and C3D8 postdose, EOT and unscheduled if clinically indicated. At the remaining time-points ECG will be collected locally (please refer to Table 8-7 and Table 8-8). The QT interval corrected by Fridericia's formula (QTcF) should be used for clinical decisions.

When triplicate ECG is required, collect three serial ECGs approximately 3 minutes apart after the participant has been resting comfortably in a supine position for about 10 minutes (it should be obtained before blood collection if a blood sample is scheduled at the same time point). Pre-dose ECG to be collected prior to any study drug dosing. Post-dose ECG to be collected at the end of study drug infusion.

Table 8-7 Central ECG collection plan

Cycle	Day	Time point *
Screening	Day -28 to Day -1	Anytime
Cycle 1	Day 1	Pre-dose[1]
	Day 8	Post-dose[2]
Cycle 3	Day 8	Post-dose[2]
EOT	N/A	Anytime
Unscheduled	Any	As clinically indicated[3]

* all ECGs to be collected in 12-lead triplicate
[1] ECG collection prior to any study drug dosing
[2] ECG collection at end of sabatolimab infusion
[3] Only required if clinically significant findings in local ECG

Table 8-8 Local ECG collection plan

Cycle	Day	Time point *
Cycle 2	1	Pre-dose

[redacted]

Cycle	Day	Time point *
Cycle 3	1	Pre-dose
Cycle 4 and subsequent cycles	1	Pre-dose

* all ECGs to be collected in 12-lead triplicate

Clinically significant ECG abnormalities present at screening should be reported on the appropriate CRF. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events. All ECGs recorded using the machines supported by the central ECG vendor must be transmitted electronically to the central ECG vendor and should be centrally reviewed by an independent reviewer. Any original ECG not transmitted electronically to the central laboratory should be forwarded for central review.

Any identifier details must be redacted e.g. participant initials, date of birth, where local regulations require it.

In case of QTcF prolongation, please refer to Section 6.5.4.4.

8.4.3 Pregnancy and 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.

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

At screening, a serum pregnancy test (serum ß-HCG) must be performed within 3 days (72 hours) before the first dose.

During the study, a urine/serum pregnancy test should be performed at Day 1 of each cycle (except Cycle 1 if a pregnancy test had been performed within 72 hours of the first dose) and a serum pregnancy test at EOT visit. Pregnancy testing (urine/serum) should occur at monthly intervals during the 150-day safety follow-up period. Refer to Table 8-1 for pregnancy testing schedule.

A positive urine pregnancy needs to be confirmed with a serum test. Confirmed positive pregnancy test requires immediate discontinuation of study treatment and discontinuation from study. See Section 10.1.4 for pregnancy reporting.

The pregnancy tests will be recorded only in the source documentation, not in the CRF.

[redacted]

Women of childbearing potential should employ the use of highly effective contraception during study treatment, for 90 days after the last dose of azacitidine, 30 days after the last dose of venetoclax (or as per their respective local labels, whichever is longer) and 150 days after the last dose of sabatolimab. Highly effective contraception methods are defined in Section 5.2.

A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner while taking azacitidine and for 3 months after stopping this drug. In addition, male participants should not donate sperm for the time period specified above.

8.4.4 Appropriateness of safety measurements

Overall, the safety assessments selected are standard for this indication/participant population.

Additionally, given the unique clinical setting and limited information about the use of sabatolimab in combination with azacitidine and venetoclax, the study employs a two part design with a halt to enrollment following the Safety run-in part of the study as explained in Section 4.1.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

The Functional Assessment of Chronic Illness Therapy Fatigue scale (FACIT-Fatigue) is a 13-item PRO measure designed to assess fatigue in people with cancer (Yellen et al 1997). It includes seven items that assess fatigue-related symptoms and six items that assess impacts of fatigue on daily activities and function over the past seven days. The higher the score, the better the quality of life. The score ranges from 0 to 52, and a score of less than 30 indicates severe fatigue.

[redacted]

All global items will be used to assign clinical meaning to observed group differences e.g., to generate clinically important difference (CID estimates) and within person change (e.g., to generate clinically important response estimates) in the on the FACIT Fatigue [redacted] total score from the participant perspective.

[redacted]

Participants will be prompted to complete all PRO questionnaires [redacted] via a provisioned ePRO device at time-points indicated in Table 8-1. At baseline, the questionnaire(s) will be completed prior to any interaction with the study investigator including any tests, treatments or receipt of results from any tests to avoid biasing participant responses to study questionnaires. The participant will be provided an ePRO device to be able to complete the PROs at home the day prior to visits to the clinic site as indicated. Please refer to the study ePRO manual for detailed instructions for completion and handling of the ePROs.

The PRO measure(s) should be completed in the order they appear on ePRO device.

8.5.2 Pharmacokinetics

Pharmacokinetic (PK), Immunogenicity (IG) [redacted] samples will be obtained and evaluated in all participants. Please refer to Table 8-9 and Table 8-10 for details on PK, IG [redacted] sample collections. If participants experience an SAE or an AE leading to the discontinuation of the study treatment, an unscheduled PK blood sample should be obtained as close as possible to the event occurrence. The date and time of the last dose and the time of PK blood draw should be recorded. If participants experience suspected immunologically related AE such as infusion-related reaction, hypersensitivity, cytokine release syndrome and anaphylaxis, an unscheduled IG blood sample should be obtained as close as possible to the event occurrence. The date and time of the last dose and the time of PK blood draw should be recorded. [redacted]

8.5.2.1 Pharmacokinetic blood collection and handling

The sabatolimab PK, [redacted] and IG blood sampling schedule is outlined in Table 8-9. A single blood sample of approximately 5 mL will be collected at each time point.

[redacted]

The venetoclax PK blood sampling schedule is outlined in Table 8-10. A single blood sample of approximately 3 mL will be collected at each time point.

Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein opposite to the arm used for infusion. When PK is collected at the same time point as ECG, the PK sample should be taken immediately after ECG.

The exact date and clock times of drug administration and blood draws for PK, IG [redacted] assessment will be recorded on the appropriate eCRF.

After permanent discontinuation of sabatolimab, the samples scheduled for pre-sabatolimab infusion should no longer be collected.

Detailed instructions for the collection procedures, handling, and shipment of sabatolimab PK, IG [redacted], and venetoclax PK samples will be provided in the [CMBG453B12203 Laboratory Manual].

Table 8-9 Sabatolimab PK, IG [redacted] blood collection log

Cycle	Day	Scheduled Time Point*	PK sample (sabatolimab)	IG sample	[redacted]
1	1	Pre-azacitidine/ venetoclax dose			
	8	Pre-sabatolimab infusion	X	X	
2	8	Pre-sabatolimab infusion	X	X	
3	8	Pre-sabatolimab infusion	X	X	
6	8	Pre-sabatolimab infusion	X	X	
9	8	Pre-sabatolimab infusion	X	X	
12	8	Pre-sabatolimab infusion	X	X	

[redacted]

Cycle	Day	Scheduled Time Point*	PK sample (sabatolimab)	IG sample	[redacted]
18	8	Pre-sabatolimab infusion	X	X	
24	8	Pre-sabatolimab infusion	X	X	
EOT[1]		Anytime	X	X	
30-Day Safety Follow-up		Anytime	X	X	
150-Day Safety Follow-up[2]		Anytime	X	X	
Unscheduled[3]		Anytime	X	X	

**All pre-dose samples should be collected within 2 hours before start of infusion*
[1] If EOT is due to reasons other than disease progression, an unscheduled PK and IG sample should also be collected at the time of confirmed disease progression.
[2] Samples at the 150 day safety follow-up visit can be collected at the Investigator's discretion if the follow-up visits are conducted at the site.
[3]Unscheduled PK and IG samples may be collected at any time if clinically indicated or at the Investigator's discretion.

Table 8-10 Venetoclax PK blood collection log

Cycle	Day	Scheduled timepoint*	PK sample (venetoclax)**
1	8	Pre-venetoclax dose	X
3	8	Pre-venetoclax dose	X

**All pre-dose samples must be collected within 30 min before dose administration*
*** Venetoclax PK samples will be collected only during Part 1 (Safety run-in) of the study*

8.5.2.2 Analytical method

Bioanalysis for pharmacokinetic studies will employ several validated assays:

· The assay to quantify sabatolimab will be a validated liquid chromatography mass spectrometry (LC-MS) assay.

· Plasma concentrations of venetoclax will be determined using a validated LC-MS assay.

· Immunogenicity testing will consist a multi-tiered ADA testing. A screening assay will be used to assess clinical samples. Samples testing positive in the screening assay will then be subjected to a confirmatory assay to demonstrate that ADAs are specific for the therapeutic

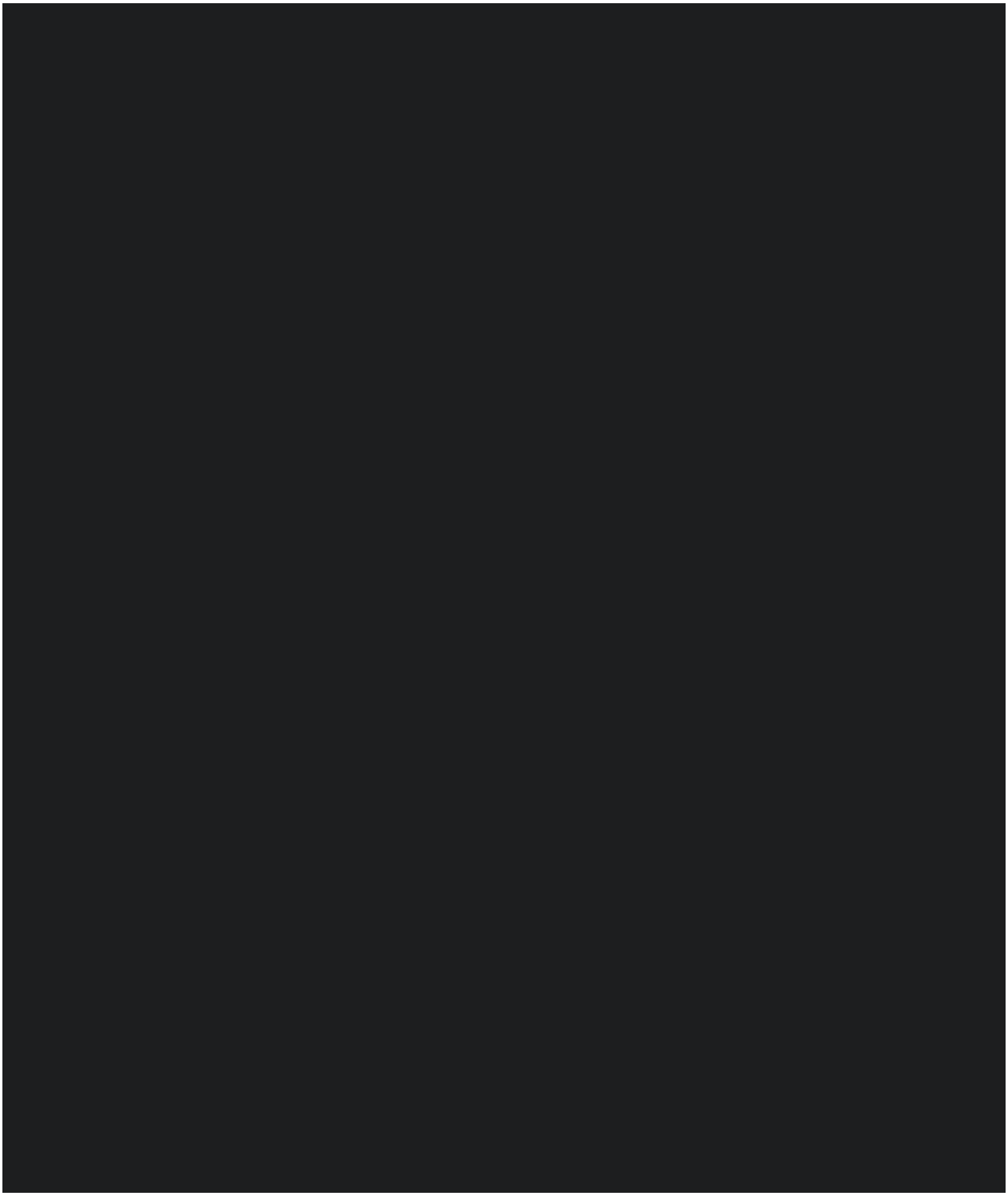
[redacted]

protein product. Samples identified as positive in the confirmatory assay will be further characterized in titration and neutralization assays.

[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

8.5.3.1 Use of residual biological samples

If participant agrees the biological samples from the bone marrow aspirate and blood collected may be used for additional studies related to sabatolimab or hematological disease/cancer, including research to help develop ways to detect, monitor or treat cancer. Those biological samples may be stored for up to 15 years after the end of the study and the decision to perform such [redacted] research studies would be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as assay availability.

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

Discontinuation of study treatment will occur when a participant meets any of the reasons described below, 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.

Study treatment must be discontinued under the following circumstances:

· Participant/guardian decision

· Pregnancy

· Use of prohibited treatment as per recommendations in the prohibited treatment section (Section 6.2.2)

· Any situation in which study participation might result in a safety risk to the participant

· Any adverse events or laboratory abnormalities that in the judgment of the investigator, taking into consideration the participant’s overall status, prevents the participant from continuing participation in the study

· Progression of disease (including transformation to acute leukemia per WHO 2016 classification, as defined as ≥20% blasts in bone marrow and/or peripheral blood),

· Termination of the study by Novartis

· Subjects who are scheduled for hematopoietic stem cell transplant (HSCT) or intensive chemotherapy at any time during the course of the study

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

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see 'Withdrawal of Informed Consent' Section 9.1.2). **Where possible, they should return for the assessments indicated in the Assessment Schedule**. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter)

[redacted]

should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

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.

The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

If discontinuation of study treatment occurs due to protocol defined reasons, participants will be followed for efficacy, safety and survival as detailed in Section 9.1.1.1, Section 9.1.1.2 and Section 9.1.1.3.

9.1.1.1 Safety follow-up

All participants must be followed for safety for 150 days after the last dose of sabatolimab or 30 days after the last dose of azacitidine or venetoclax whichever is longer.

After the 30-Day on-site safety follow-up visit, participants will be followed via telephone call (or on-site visit if participant happens to be visiting the site) at 90 and 150 days after the last dose of sabatolimab. All safety assessments should be completed as per Table 8-1. However, if the participant begins new antineoplastic medication before the end of the safety follow-up period, the collection of new SAEs and AEs unrelated to study medication will stop and thereafter only suspected AEs and suspected SAEs will continue to be collected up to the end of the safety follow-up period. For female participants of childbearing potential, a pregnancy test will be performed at the timepoints listed in Table 8-1.

9.1.1.2 Post-treatment follow-up

For participants who discontinue treatment for reasons other than disease progression, death, lost to follow-up, or withdrawal of consent; efficacy assessments, and other required assessments will continue to be performed as per the assessment schedule (see Table 8-1) until disease progression, death, lost to follow-up, or withdrawal of consent.

9.1.1.3 Survival follow-up

Participants will enter the survival follow-up period in parallel with the safety follow-up or efficacy follow-up periods. Participants will then be contacted by telephone every 12 weeks to follow-up on their survival status. Any new antineoplastic therapies that have been started since the previous contact will be collected. HSCT information will also be collected during these phone calls.

9.1.1.4 Replacement policy

Participants will not be replaced on study. However, if a participant is considered as non-evaluable for the Safety run-in (Part 1) (see Section 6.5.1), enrollment of a new participant to the Safety run-in will be considered if there are less than the required number of evaluable participants.

[redacted]

9.1.2 Withdrawal of informed consent

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a participant:

- Does not want to participate in the study anymore,

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

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 his/her consent and record this information.

Where consent to the use of personal and coded data is not required, participant therefore cannot withdraw consent. They still retain the right to object to the further use of 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.

All efforts should be made to complete the assessments prior to study discontinuation. A final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table.

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation.

For United States (US): All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For European Union (EU) and Rest of World (RoW): All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

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 or withdraw, 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.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/risk assessment of participating in the study, practical reasons (including

slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible to perform their End of Treatment Visit (EOT) and the assessments for EOT as described in Table 8-1 and will be treated as a prematurely withdrawn participant. 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 the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

In the event that the study is terminated prematurely, e.g. based on recommendation of the steering committee (see also Section 10.2.2), participants still receiving study treatment and who, according to investigator assessment, continue to benefit from the treatment, will be offered to complete study treatment as per protocol or through an alternate setting (see Section 9.2).

9.2 Study completion and post-study treatment

Following completion of the safety follow-up period and/or efficacy follow-up period, all participants will be followed for survival (see Section 9.1.1.3).

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.

The CR rate analysis will be conducted after the last participant enrolled has completed 6 cycles of treatment or discontinued earlier. Following the cut-off date for the analysis reported in the primary Clinical Study Report (CSR), the study will remain open and ongoing participants will continue to receive study treatment and be followed per the schedule of assessments until discontinuation criteria is met per Section 9.1.1.

The end of study is defined as the earliest occurrence of one of the following:

· Last participant has been followed for at least 3 years or have discontinued treatment, have died, have been lost to follow-up or have withdrawn consent to further participation in the study.

· The last participant on treatment has been enrolled into a separate rollover study or another option of continued treatment with sabatolimab.

At the end of the study, in alignment with local regulations, Post Trial Access (PTA) will be set-up to provide sabatolimab outside this study through an alternative setting for participants who are still receiving treatment with sabatolimab and deriving clinical benefit in the opinion of the investigator (see Section 6.1.5).

The final analysis will occur at the end of the study. All available data from all participants up to this cut-off date will be analyzed and summarized in a final CSR.

10 Safety monitoring and reporting

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 participant or 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 AEs must be sought by non-directive questioning of the participant at each visit during the study. AEs 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):

Adverse events will be assessed and graded according to:

1. the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

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 if the event is ongoing, an outcome of not recovered/not resolved 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/withdrawn

[redacted]

· its outcome (i.e. recovery status or whether it was fatal)

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

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

Adverse event monitoring should be continued for at least:

· 150 days after the last administration of sabatolimab, or 30 days after the last administration of azacitidine, or 30 days after the last administration of venetoclax, whichever is later.

OR

· until the start of a new post treatment antineoplastic medication if sooner than the 150 days mentioned above. If a participant starts post treatment antineoplastic medication, then only adverse events suspected to be related to study treatment should be collected, up to 150 days after discontinuation of sabatolimab.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as separate adverse event.

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.

Adverse events separate from the progression of malignancy (i.e. deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

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 participants with the underlying disease.

[redacted]

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 in participant 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 out participant 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 and the malignant neoplasm is not a disease progression of the study indication.

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.

[redacted]

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until the end of the safety follow-up period (Section 9.1.1.1), must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

SAE reporting timeframes:

1. Screen Failures (e.g. a participant who is screened but is not treated): All SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.

2. Treated participants SAEs collected between time participant signs ICF until 30 days after the participant has discontinued or stopped azacitidine or venetoclax or 150 days after stopping sabatolimab, whichever is later. If a participant starts post treatment antineoplastic medication, then only SAEs suspected to be related to study treatment must be collected, up to 150 days or beyond after discontinuation of sabatolimab.

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, and under no circumstances later than within 24 hours of the investigator receiving the follow-up information. 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 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 participant has completed the safety follow-up period should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her 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 for 12 months after the estimated date of delivery 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 participant Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

For all pregnancies with live birth and/or unknown outcome the newborn has to be followed up to obtain infant health status and development up to twelve months after delivery.

Pregnancy outcomes will not be collected for the female partners of any males who took study treatment in this study.

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 CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE (see Table 10-1). 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 CRF (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 Data Monitoring Committee

A Data Monitoring Committee (DMC) will not be required for this study considering that it is open-label single-arm study. However, close monitoring of safety is planned; specifically, Novartis and the study investigators involved in the Safety run-in (Part 1) will conduct at least one safety review meeting for each cohort: once all evaluable participants in that cohort are observed for at least 2 cycles of treatment or experienced a DLT, whichever occurs first, in order to review and discuss safety data, including adverse events, dose interruptions and dose modifications, as well as available pharmacokinetic data. At each planned safety review meeting, Novartis and the investigators must reach a consensus based on the available safety and clinical pharmacology data, to decide whether to continue with enrollment on the study.

10.2.2 Steering Committee

The steering committee (SC) will be established comprising investigators participating in the trial, i.e. not being Novartis representatives from the Clinical Trial Team. The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. During the Safety run-in (Part 1) the SC will review the safety data during the planned safety reviews. Thereafter, during the Expansion (Part 2), the SC will review periodically the safety data, at least approximately every 6 months. After each safety review, the SC will make recommendations on the study conduct (including study termination). The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the SC will be defined in a Steering Committee charter.

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 on CRFs) (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.

[redacted]

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification. **In addition to data entered into the eCRF, requisition forms may also need to be completed for (e.g. PK, [redacted] etc.) sample collection.**

11.2 Database management and quality control

Novartis personnel 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.

Kit numbers and data about sabatolimab, venetoclax and azacitidine dispensed to the participant and all dose interruptions (for sabatolimab only) will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis at specific timelines.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis development management.

Samples collected for all third party data such as biological samples (including PK, IG, [redacted]) and ECGs will be processed centrally and the results will be sent electronically to Novartis.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE or 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. Continuous remote monitoring of each site's data may be performed by a centralized Novartis or delegated CRO CRA organization. Additionally, a central analytics organization may analyze data, identify risks and trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

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

[redacted]

assessments. All information on CRFs 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 CRFs 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

For each cohort of the safety run-in part, the primary safety analysis will be conducted when the evaluable participants would have been observed for 2 cycles of treatment. If the dose of 400 mg of sabatolimab in combination with azacitidine and venetoclax with at least 3 evaluable participants is judged to be safe, then at least 9 new evaluable participants would be needed to evaluate the safety of the 800 mg of sabatolimab in combination with azacitidine and venetoclax. Otherwise, the study will be stopped. If the 800 mg of sabatolimab is not meeting overdose criteria, Expansion (Part 2) of the study will be opened. Otherwise study will be stopped.

The primary efficacy analysis (CR rate analysis) will be performed on all participant data treated at dose level of 800 mg of sabatolimab at the time last enrolled participant will have completed at least 6 cycles of treatment or discontinued earlier.

The final efficacy and safety analyses will be conducted when last enrolled participant have been followed up for at least 3 years (see Section 9.2 for details).

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

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.

12.1 Analysis sets

The Full Analysis Set (FAS) comprises all participants who received at least one dose of study treatment.

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

The Dose Determining Set (DDS) includes all participants from the FAS enrolled the Safety run-in part who met the minimum exposure criterion and had sufficient safety evaluations, or experienced a dose limiting toxicity (DLT) during the first 8 weeks of dosing (two cycles).

A participant has met the minimum exposure criterion if the participant has received during the first 2 cycles 2 infusions of sabatolimab at the assigned dose level in Q4W dosing regimen, and has taken at least 75 % of the planned dose of azacitidine and venetoclax (i.e. for 2 cycles: 11

doses of azacitidine out of the 14 doses planned and 21 doses of venetoclax out of the 28 doses planned).

Participants who do not experience a DLT during Cycles 1 and 2 are considered to have sufficient safety evaluations if they have been observed for at least 56 days following the first dose, and are considered by both the sponsor and investigators to have enough safety data to conclude that a DLT did not occur.

The sabatolimab and venetoclax pharmacokinetic analysis sets include all participants from the Safety Set who provide at least one evaluable sabatolimab/venetoclax PK concentration.

For a concentration to be evaluable:

- Dosing information must be properly documented (data and time of administration).
- For pre-dose samples: the sample is collected before the next dose administration.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively for all participants from the FAS. These data will be summarized by dose level of sabatolimab for the safety run-in part and for participants entering the expansion part.

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.

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 to study treatment as well as each study treatment component (sabatolimab (mg), venetoclax (mg) and azacitidine (mg)) as well the dose intensity by cycle (mg/day) (derived as the ratio of actual cumulative dose and planned dose intensity per cycle) and the relative dose intensity (%) by cycle (derived as the ratio of dose intensity and planned dose intensity) will be summarized by descriptive statistics.

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

The number of participants with dose adjustments (reductions, interruptions or permanent discontinuation) for each study treatment component and the reasons will be summarized. All exposure data will be listed.

[redacted]

12.4 Analysis of the primary endpoint(s)

The primary objective of the Safety run-in (Part 1) of the study is to determine whether sabatolimab 400 mg and 800 mg are safe (i.e. not meeting overdose criteria) when added in combination with azacitidine and venetoclax.

The primary objective of the Expansion (Part 2) is to determine the complete remission rate (CR) of sabatolimab (800 mg Q4W) in combination with azacitidine and venetoclax. This analysis will include all participants' data from cohort 2 of the Safety run-in (Part 1) and Expansion (Part 2).

12.4.1 Definition of primary endpoints and estimands

12.4.1.1 Safety run-in (Part 1)

For the Safety run-in part, the primary endpoint is the incidence of DLTs in the first 2 cycles of treatment for participants in the DDS.

12.4.1.2 Cohort 2 of Safety run-in (Part 1) and Expansion (Part 2)

The primary clinical question of interest is the following:

Is Sabatolimab 800 mg Q4W in combination with fixed doses of azacitidine (75 mg/m^2 Day 1-7) and venetoclax (400 mg Day 1-14) associated with improved efficacy (i.e. CR rate >= 50%) for participants with high or very high risk MDS?

The primary endpoint (combining data from cohort 2 of the Safety run-in (Part 1) and the Expansion (Part 2) (i.e. sabatolimab 800 mg (Q4W)) is the proportion of participants achieving a complete remission (CR) as per investigator assessment (Section 2 and Table 2-1).

The primary efficacy estimand is described by the following five attributes:

- **Population:** Adult participants not eligible for intensive chemotherapy nor for HSCT with high or very high risk MDS (IPSS-R criteria (Greenberg et al 2012)) as assessed locally by the investigator.
- **Variable:** Best overall response among all disease response assessments as assessed by investigator per modified IWG MDS criteria (Cheson et al 2006) up to new anti-cancer therapy (including HSCT).
- **Treatment:** Study treatment is sabatolimab 800 mg Q4W + azacitidine (75 mg/m^2 Day 1-7) + venetoclax (400 mg Day 1-14). Participants will continue treatment until a reason of treatment discontinuation is met (e.g. progression, unacceptable toxicity, HSCT) (Section 6.1.5).
- **Intercurrent events:**
  - **Study treatment modification:** all CR will be taken into account regardless of any study treatment component interruption, dose adjustment or permanent discontinuation (Section 6.1.5).
  - **Concomitant medications and supportive care:** A participant may receive blood transfusion as supportive care and prophylactic treatment as clinically indicated (e.g. antiemetics, antibiotics, antifungals, Section 6.2.1). All CR will be taken into account

regardless of any concomitant medication administration including prohibited medications.

- **New anti-cancer therapy/HSCT**: CR achieved after initiation of a new anti-cancer therapy or HSCT will not be taken into account.

- **Summary measures:** The CR rate and the 95% confidence interval (CI).

12.4.2 Statistical model, hypothesis, and method of analysis

12.4.2.1 Safety run-in (Part 1)

Dose Limiting Toxicities (DLT) analysis

Assessment of sabatolimab 400 and 800 mg (4QW) not meeting overdose criteria when added to azacitidine and venetoclax will be based on the estimation of the probability of DLT in the first 2 cycles (starting from Cycle 1 Day 8) for participants in the DDS.

The assessment in Safety run-in (Part 1) will be guided by a Bayesian analysis of DLT data for sabatolimab, azacitidine and venetoclax in the first 2 cycles (starting from Cycle 1 Day 8) of treatment. The probability of DLT is modeled using a Bayesian approach detailed in Section 16.1.

After each cohort, the posterior distributions for the risk of DLT will be summarized to provide the posterior probability that the risk of excessive toxicity (DLT rate >=33%) is less than 25%.

The escalation with overdose control (EWOC) principle

Dosing decisions are guided by the escalation with overdose control principle (Rogatko et al 2007). A combination dose will be judged to be safe if the risk of excessive toxicity at that combination dose is less than 25%.

Prior information

A meta-analytic framework approach was used to derive the prior distribution for the single-agent sabatolimab, azacitidine and venetoclax model parameters. The prior for the logistic model parameters for this study is the conditional distribution of the parameters given the historical data (see Spiegelhalter 2004, Neuenschwander 2010, Neuenschwander 2014). Priors are derived from hierarchical models, which take into account possible differences between the studies.

A full description of the application of the meta-analytic framework approach to derive the prior distributions of the single agent sabatolimab, azacitidine and venetoclax model parameters is given Section 16.

The prior distributions for the interaction parameters were based upon prior understanding of possible drug safety interactions. These priors are fully described in Appendix Section 16.

Listing of DLTs

DLTs will be listed, and their incidence summarized by primary system organ class and worst grade (CTCAE version 5.0) Listings and summaries will be based on the DDS.

[redacted]

The Section 16.1 provides details of the statistical method and the probability of excessive toxicity for different scenarios in the Safety run-in (Part 1).

12.4.2.2 Cohort 2 of Safety run-in (Part 1) and Expansion (Part 2)

CR primary analysis

The CR primary analysis will be performed for participants from cohort 2 of Safety run-in (Part 1) and Expansion (Part 2) treated with sabatolimab 800 mg Q4W.

A Bayesian design will be used in order to estimate the CR rate in the FAS (Full Analysis Set) and to provide inferential summaries (e.g., mean, median, standard deviation, 95% credible intervals, and interval probabilities) based on Bayesian posterior distribution of the CR rate. Assuming a non-informative prior distribution (Beta(1,1)), the distribution of the CR rate will be updated with all available data from the participants included in the FAS.

The decision criteria for trial success are the following:

- Posterior median of CR rate is ≥ 50% and
- Posterior probability that CR rate is > 39% is at least 97.5%.

The cumulative posterior distribution will be used to derive the probability that the true CR rate is superior to 50%. Based on preliminary efficacy data observed with the combination azacitidine + venetoclax (Wei et al 2019), a 50% CR rate is a reasonable threshold to be considered in this specific setting.

The results will be also presented with a frequentist formulation. The CR rate and the exact 95% confidence interval (CI) (Clopper CJ and Pearson ES 1934), as well as the 1-sided p-value will be provided on the FAS. The test will be performed using an overall one-sided 2.5% level of significance. Thus, the null hypothesis (H_0:CR ≤ 39%) will be rejected if the lower bound of the two-sided 95% exact CI is >39%.

The analysis will be performed using data up to the analysis data cut-off date, which will be 6 cycles after the last participant is enrolled.

12.4.3 Handling of remaining intercurrent events of primary endpoint

For the primary analysis, only CR assessments after first dose of study treatment and prior start of any other anti-neoplastic therapy or HSCT are considered. An adequate response assessment is considered any disease assessment indicating response status apart from “unknown” or “not done”.

12.5 Analysis of secondary endpoints

The secondary objectives are to assess the overall response rate (ORR), CR/mCR rate, duration of CR, time to response, time to CR/mCR, duration of response, duration of CR/mCR, overall survival (OS), event free survival (EFS), progression free survival (PFS), leukemia free survival (LFS), RBC/platelets transfusion independence, changes from baseline in fatigue, pharmacokinetic and safety.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

12.5.1.1 Safety run-in (Part 1)

CR+mCR rate

CR+mCR rate is defined as the proportion of participants with best overall response of either complete remission (CR) or marrow complete remission as per investigator assessment (Table 8-3). CR/mCR rate will be provided with exact 95% confidence interval (Clopper CJ and Pearson ES 1934).

CR/mCR will be provided by dose level of sabatolimab.

Overall Response Rate (ORR)

ORR rate is defined as the proportion of participants with best overall response of hematological improvement (HI) or better as per investigator assessment (Table 8-3). ORR rate will be provided with exact 95% confidence interval (Clopper CJ and Pearson ES 1934).

ORR will be provided by dose level of sabatolimab.

Improvement of RBC/platelets transfusion independence

Red blood cells (RBC)/Platelets transfusion independence rate is defined as the proportion of participants having received no RBC/Platelets transfusions during at least 8 consecutive weeks (see Section 8.3.1 for details).

The number and percentage of participants will be shown for the overall FAS and then also in only those with transfusion dependence at baseline (i.e ≥ 3 units of transfusion within 8 consecutive weeks prior to start of treatment).

Percentages will be provided with exact 95% confidence intervals (Clopper CJ and Pearson ES 1934). For participants with at least one period of transfusion independence, the total duration of all transfusion independence periods will be also summarized.

The duration of the transfusion independence is defined from the end date of the last transfusion received until the date transfusions are given again or last treatment in case transfusions had not (re-)started during treatment.

The data will be summarized by dose level of sabatolimab.

Immunogenicity analysis

Immunogenicity will be characterized descriptively by tabulating ADA prevalence at baseline and ADA incidence on-treatment. The data will be summarized by dose level of sabatolimab.

12.5.1.2 Cohort 2 of Safety run-in (Part 1) and Expansion (Part 2)

CR+mCR rate

CR+mCR rate is defined as the proportion of participants treated with sabatolimab at 800 mg Q4W with best overall response of either complete remission (CR) or marrow complete remission as per investigator assessment (Table 8-3). CR/mCR rate will be provided with exact 95% confidence interval (Clopper CJ and Pearson ES 1934).

[redacted]

Overall Response Rate (ORR)

ORR rate is defined as the proportion of participants treated with sabatolimab at 800 mg Q4W with best overall response of hematological improvement (HI) or better as per investigator assessment (Table 8-3). ORR rate will be provided with exact 95% confidence interval (Clopper CJ and Pearson ES 1934).

Duration of CR

The duration of CR will be derived for participants treated with sabatolimab at 800 mg Q4W who achieve CR per modified IWG-MDS CHeson 2006 (prior to any new antineoplastic therapy, including HSCT) as per investigator assessment and is defined from the first occurrence of CR until relapse, progression or death due to any reason. Relapse, disease progression or death occurring after HSCT will be considered as event for the duration of CR. The date of the event will be the date of relapse, progression, death whichever occurs first. If participant did not relapse nor progressed/died, the duration of response will be censored at last adequate response assessment. If the participant has started a new antineoplastic therapy without prior documented relapse or progression, the duration of CR is censored at last adequate assessment prior to start of that therapy and thus any subsequent relapse/ progression /death not considered an event for duration of CR.

Two supplementary analyses will be performed in which (a) new antineoplastic therapy and HSCT will not be censored and not counted as an event, and (b) start of new antineoplastic therapy will be considered as an event and HSCT will not be censored and not be counted as an event.

Duration of CR will be estimated using the Kaplan-Meier Method. The median duration of CR along with 95% Confidence interval will be presented.

Duration of CR/mCR

The duration of CR/mCR will be derived for participants treated with sabatolimab at 800 mg Q4W who achieve CR or mCR (prior to any new antineoplastic therapy, including HSCT) as per investigator assessment and is defined from the first occurrence of CR or mCR until relapse, progression or death due to any reason. Relapse, progression or death occurring after HSCT will be considered as event for the duration of CR/mCR. The date of the event will be the date of relapse, progression, death whichever occurs first. If participant did not relapse nor progressed/died, the duration of CR/mCR will be censored at last adequate response assessment. If the participant has started a new antineoplastic therapy without prior documented relapse or progression, the duration of CR/mCR is censored at last adequate assessment prior to start of that therapy and thus any subsequent relapse/ progression /death not considered an event for duration of CR/mCR.

Two supplementary analyses will be performed in which (a) new antineoplastic therapy and HSCT will not be censored and not counted as an event, and (b) start of new antineoplastic therapy will be considered as an event and HSCT will not be censored and not be counted as an event.

Duration of CR/mCR will be estimated using the Kaplan-Meier Method. The median duration of CR/mCR along with 95% Confidence interval will be presented.

[redacted]

Duration of response

The duration of response will be derived for participants treated with sabatolimab at 800 mg Q4W who achieve HI or better (prior to any new antineoplastic therapy, including HSCT) as per investigator assessment and is defined from the first occurrence of CR, mCR, PR or HI until relapse, progression or death due to any reason.

Relapse, progression or death occurring after HSCT will be considered as event for the duration of response. The date of the event will be the date of relapse, progression, death whichever occurs first. If participant did not relapse nor progressed/died, the duration of response will be censored at last adequate response assessment. If the participant has started a new antineoplastic therapy without prior documented relapse or progression, the duration of response is censored at last adequate assessment prior to start of that therapy and thus any subsequent relapse/ progression /death not considered an event for duration of response.

Two supplementary analyses will be performed in which (a) new antineoplastic therapy and HSCT will not be censored and not counted as an event, and (b) start of new antineoplastic therapy will be considered as an event and HSCT will not be censored and not be counted as an event.

Duration of response will be estimated using the Kaplan-Meier method. The median duration of response along with 95% confidence interval will be presented.

Time to CR/mCR

The time to CR/mCR will be derived for all participants treated with sabatolimab at 800 mg Q4W and is defined from start of treatment to first occurrence of CR/mCR (prior to any new antineoplastic therapy, including HSCT). For participants who reached CR /mCR after HSCT or a new antineoplastic therapy, the time to CR/mCR will be censored at time of HSCT or initiation of new antineoplastic therapy.

Participants who did not reach CR/mCR will be censored at last adequate response assessment. For participants who progressed, died or the disease progressed to acute myeloid leukemia, the time to CR/mCR will be censored at maximum follow-up (last participant last visit).

Time to CR/mCR will be estimated using the Kaplan-Meier method. The median time to CR/mCR along with 95% confidence interval will be presented.

Event-free survival (EFS)

Event-free survival (EFS) is defined from the date of start of treatment to:

- Lack of complete remission within the first 6 cycles of start of treatment
- Progression/Relapse
- Death from any cause

whichever occurs first.

Participants treated with sabatolimab at 800 mg Q4W who failed to achieve CR within 6 cycles of treatment will have their EFS event documented at start of treatment. If participant discontinued treatment due to any reason (including death) prior to 6 cycles and without CR will be considered as EFS event documented at start of treatment date.

[redacted]

Progression/Relapse, death events after HSCT and transfusion of blood products will be taken into account. However, Progression/Relapse, death occurring after initiation of new antineoplastic therapy will not be considered as event and EFS will be censored at last adequate response assessment.

In case of two or more missing assessments prior to documented progression, relapse or death, EFS will be censored at the last adequate response assessment prior to the documentation of relapse or death.

EFS will be estimated using the Kaplan-Meier method. The median EFS along with 95% confidence interval will be presented.

Progression free survival (PFS)

PFS is defined as the time from start date of treatment to date of relapse, progression (including transformation to acute leukemia per WHO 2016 classification) or death due to any cause. If a participant is not known to have relapsed progressed nor died, PFS will be censored at the last adequate response assessment (on or before the cut-off date). Progression/relapse or death after HSCT, interruptions, or discontinuation of study treatment due to any reason will be taken into account. However, Progression/Relapse, death occurring after initiation of new antineoplastic therapy will not be considered as event and PFS will be censored at last adequate response assessment.

In case of two or more missing assessments prior to documented progression, relapse or death, PFS will be censored at the last adequate response assessment prior to the documentation of progression, relapse or death.

PFS will be estimated using the Kaplan-Meier method. The median PFS along with 95% confidence interval will be presented.

Leukemia free survival (LFS)

LFS is defined as the time from start of treatment to transformation to acute leukemia as per investigator assessment defined as the following:

- ≥ 20% blasts in bone marrow/ peripheral blood (per WHO 2016 classification)
- Diagnosis of extramedullary acute leukemia
- Death due to any cause

whichever occurs first.

If a participant is known to not have progressed to leukemia, then LFS will be censored at the last bone marrow/peripheral blood assessments (on or before the cut-off date). All of three events (≥ 20% blasts in bone marrow/peripheral blood, diagnosis of extramedullary acute leukemia or death) after HSCT, interruptions, or discontinuation of study treatment due to any reason will be taken into account. However, events occurring after initiation of new antineoplastic therapy will not be considered as event and LFS will be censored at last assessment of bone marrow/peripheral blood, diagnosis of extramedullary acute leukemia or survival follow-up prior to initiation of new antineoplastic therapy.

LFS will be estimated using the Kaplan-Meier method. The median LFS along with 95% confidence interval will be presented.

[redacted]

Overall Survival (OS)

OS is defined as the time from start date of treatment to date of death due to any cause. If a participant is not known to have died, then OS will be censored at the latest date the participant was known to be alive (on or before the cut-off date). All deaths will be taken into account whenever the death occurred, i.e. even after new anti-neoplastic therapy, HSCT, interruptions, or discontinuation of study treatment due to any reason.

OS will be estimated using the Kaplan-Meier method. The median OS along with 95% confidence interval will be presented.

Improvement of RBC/platelets transfusion independence

Red blood cells (RBC)/Platelets transfusion independence rate is defined as the proportion of participants having received no RBC/Platelets transfusions during at least 8 consecutive weeks (see Section 8.3.1 for details).

The number and percentage of participants will be shown for the overall FAS and then also in only those with transfusion dependence at baseline (i.e ≥ 3 units of transfusion within 8 consecutive weeks prior to start of treatment).

Percentages will be provided with exact 95% confidence intervals (Clopper CJ and Pearson ES 1934). For participants with at least one period of transfusion independence, the total duration of all transfusion independence periods will be also summarized.

The duration of the transfusion independence is defined from the end date of the last transfusion received until the date transfusions are given again or last treatment in case transfusions had not (re-)started during treatment.

Immunogenicity analysis

Immunogenicity will be characterized descriptively by tabulating ADA prevalence at baseline and ADA incidence on-treatment.

12.5.1.3 Expansion (Part 2)

MDS symptoms and fatigue

The following analyses will be performed:

- Changes from baseline to post-baseline in fatigue using the FACIT-Fatigue [redacted].

12.5.2 Safety endpoints

Safety analyses will be summarized for the safety set of the Safety run-in (Part 1) and Expansion (Part 2). Safety data will be provided by dose level of sabatolimab in the Safety run-in part.

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

[redacted]

The overall observation period will be divided into three mutually exclusive segments:

1. Pre-treatment period: from day of participant's informed consent to the day before first administration of study treatment

2. On-treatment period: from date of first administration of study treatment to 30 days after date of last administration of study treatment

3. Post-treatment period: any observation starting at day 31 after last administration of study treatment

An overall safety period will be defined from date of first administration of study treatment to 150 days after the last dose of sabatolimab.

Adverse events

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period. The number (and percentage) of participants with treatment emergent adverse events will be summarized 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.

Serious adverse events and non-serious adverse events will be tabulated. All deaths (on-treatment and post-treatment) will be summarized.

In addition, all AEs and SAEs which started during the overall safety period will be summarized. All reported AEs will be listed and those that started during the pre-treatment, overall safety period and post-treatment period will be flagged.

Vital signs

All vital signs abnormalities will be summarized by visit.

12-lead ECG

HR PR, and QTcF will be obtained from 12-lead ECGs for each participant at screening and during the study. ECG data will be read and interpreted centrally.

Categorical analysis of QTcF interval and HR data will be based on the summary of number of participants meeting or exceeding predefined limits.

Clinical laboratory evaluations

Grading of laboratory values will be assigned programmatically as per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher.

For laboratory tests where grades are not defined by CTCAE version 5.0, results will be categorized as low/normal/high based on laboratory normal ranges.

[redacted]

For laboratory tests where grades are defined by CTCAE v5.0:

- Shift tables using CTCAE v5.0 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE v5.0:

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value

Other safety evaluations

ECOG PS

ECOG PS will be summarized at each timepoint during the study.

12.5.3 Pharmacokinetics

The respective Pharmacokinetic Analysis Set (PAS) for sabatolimab and venetoclax from Safety run-in (Part 1) and Expansion (Part 2) will be used in all pharmacokinetic data analysis.

Sabatolimab and venetoclax drug concentrations

Sabatolimab and venetoclax concentration data will be listed by participant, and visit/sampling time point. Descriptive summary statistics for sabatolimab and venetoclax concentrations will be provided by visit/sampling time point. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum, as well as the frequency (n, %) of concentrations below the lower limit of quantification (LLOQ) and reported as zero. Values below the LLOQ will be treated as missing for the calculation of the geometric means and geometric CV%. PK parameters (the minimum observed plasma or serum drug concentration (Cmin or Ctrough) will be estimated and reported. Missing values for any PK parameters or concentrations will not be imputed and will be treated as missing.

All concentration data for sabatolimab and venetoclax vs. time profiles will be displayed graphically.

As the half-life of venetoclax is approximately 26 hours, the sample collected at Cycle 1 Day 8 will be considered as the baseline venetoclax concentration at steady state before any dose administration of sabatolimab. The impact of sabatolimab on the venetoclax concentrations may be assessed by comparing concentrations before and after sabatolimab.

Population pharmacokinetic analysis

If data permit, a mixed-effects model may be applied to the serum sabatolimab concentration-time data from this study along with other studies to generate post-hoc estimates of pharmacokinetic parameters using appropriate software to characterize sabatolimab exposure and to determine the effects of intrinsic (i.e. demographic factors) and extrinsic covariates (e.g. combination partners) on sabatolimab exposure. If there is sufficient data for analysis, the details of the population pharmacokinetic analyses may be provided in a separate reporting and analysis plan, and the results may be reported in a separate population pharmacokinetic report.

[redacted]

[redacted]

12.7 Interim analyses

No formal interim analysis is planned for this trial. During the Expansion (Part 2), a periodic safety review by the Steering Committee will occur approximately every 6 months.

In the Safety run-in (Part 1), the first safety review meeting will be conducted after participants included in the first cohort (N=6 with at least 3 evaluable participants treated with sabatolimab at the 400 mg Q4W) have completed 2 cycles of treatment. If the 400 mg Q4W dose of sabatolimab is considered to be safe in combination with venetoclax and azacitidine guided by the Bayesian analysis based on the incidence of dose limiting toxicity (DLT) data as well as all available safety, clinical pharmacology and tolerability data a second cohort with 12 participants will be opened (sabatolimab at 800 mg Q4W), otherwise the study will be stopped.

After completion of 2 cycles of treatment with at least 9 evaluable participants, the second safety review meeting will take place. The decision will be made based on DLT observation and the Bayesian model to open the Expansion (Part 2) (or not) at this dose level (sabatolimab at 800 mg Q4W) in combination with venetoclax and azacitidine. If sabatolimab 800 mg Q4W is considered to be safe then Expansion (Part 2) will be opened at the same dose level (800 mg Q4W). Otherwise the study will be stopped.

The primary analysis on CR rate will be performed after last participant have completed 6 cycles of treatment with sabatolimab + azacitidine + venetoclax or discontinued earlier. A final analysis will be performed after last enrolled participant have been followed for 3 years or discontinued study earlier. Formal testing of the primary endpoint with full level alpha will be performed at the primary analysis. If required or requested by Health Authorities, updated analyses after the primary CR rate analysis may be conducted prior to the final analysis.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

12.8.1.1 Safety run-in (Part 1)

No formal statistical power calculations to determine sample size were performed for this part of the study. In case the starting dose (sabatolimab 400 mg Q4W (N=6)) with the fixed dose combination of azacitidine plus venetoclax is confirmed to be safe and tolerated for at least 3 evaluable participants, another cohort will be opened at 800 mg of sabatolimab Q4W (N=12) with fixed dose of venetoclax plus azacitidine with at least 9 evaluable participants. Otherwise, the study will be stopped.

In total, the Safety run-in (Part 1) is expected to enroll approximately 18 participants (6 participants for cohort 1 (Sabatolimab (400 mg Q4W) and 12 participants for cohort 2 (800 mg (Q4W)) in order to have at least 12 evaluable participants (3 evaluable participants in cohort 1 and 9 evaluable participants in cohort 2).

12.8.1.2 Cohort 2 of Safety run-in (Part 1) and Expansion (Part 2) (CR primary analysis)

The sample size calculation is based on the Complete Remission (CR) rate (primary efficacy endpoint) for participants treated with sabatolimab 800 mg Q4W from Safety run-in (Part 1)

and Expansion (Part 2). The hypotheses to be tested and details of the testing strategy are described in Section 12.4.2.

Based on available data (Wei et al 2019), the CR rate with the combination azacitidine and venetoclax is expected to be around 39%. The first criteria to declare the trial successful is to test if the CR rate with sabatolimab in combination with azacitidine and venetoclax is at least 50% (statistical significance).

The Bayesian formulation of this dual criterion design can be expressed as below:

- Bayesian statistical significance: probability for a positive treatment effect (i.e. CR rate > 39% | data) ≥ 0.975.
- Clinical relevance: posterior median of CR rate ≥ 50%.

With two criteria stated above the minimally required sample (n_{min}) size is 67 and the sample size was set to 70 including participants from cohort 2 of the Safety run-in (Part 1) and the Expansion (Part 2) and thus 76 for the total sample size (including the 6 participants treated at 400 mg Q4W in the cohort 1 of the Safety run-in (Part 1). For 70 participants (included for the primary efficacy analysis), the table below shows data scenarios (number of participant achieving complete remission) with respective inferential results and decisions.

The minimum number of participants with CR to declare this trial successful (both statistical significance and clinical relevance met) is 36 out of 70 participants (51.4%).

Based on simulations (Table 12-1), a total of 36 responders out of 70 participants is required for trial success, with estimates of 51.4% for the posterior median CR rate and 98.3% for the posterior probability for a positive effect (CR>39%). If the number of participants with CR is less than 36, both criteria are not met (NO-GO).

Table 12-1 Data scenarios, inferential results and decisions (n=70)

True CR rate	Posterior median CR	Posterior probability for a positive effect (CR>39%)	Decision for trial success
30/70 (42.9%)	43.0%	0.754	Failed
31/70 (44.3%)	44.4%	0.823	Failed
32/70 (45.7%)	45.8%	0.879	Failed
33/70 (47.1%)	47.2%	0.920	Failed
34/70 (48.6%)	48.6%	0.950	Failed
35/70 (50.0%)	50.0%	0.970	Failed
36/70 (51.4%)	51.4%	0.983	Successful

A non-informative Beta (1,1) prior with mean 50% has been used in these calculations.

Operating characteristics for various true CR rates are presented in the table below. The type-I error under the null value (CR rate = 38.6%) is 2.0% and power is 80% assuming a true CR of 55.7 %.

Table 12-2 Operating characteristics for true CR rate (n=70)

True CR rate	Probability of success (Go)	Probability of futility (No Go)
27/70 (38.6%)*	0.020	0.980
28/70 (40.0%)	0.035	0.965
29/70 (41.4%)	0.056	0.944
30/70(42.9%)	0.094	0.906
31/70 (44.3%)	0.140	0.860
32/70 (45.7%)	0.204	0.796
33/70 (47.1%)	0.272	0.728
34/70 (48.6%)	0.355	0.645
35/70 (50%)	0.452	0.548
36/70 (51.4%)	0.546	0.454
37/70 (52.9%)	0.644	0.356
38/70 (54.3%)	0.721	0.279
39/70 (55.7%)**	0.800	0.200

*For a true CR rate of 38.6% (null value), the probability for a trial success is 2.0% (*type-I error)*. **For a true CR rate of 55.7%, the probability for a trial success is 80% (*power*). These calculation were made using the software R (version 3.6.1) using the RBestT package.

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.

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.

[redacted]

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16 Appendices

16.1 Appendix 1: Statistical considerations for Safety run-in Part

This appendix provides details of the statistical model, the derivation of prior distributions from historical data, the results of the Bayesian analyses and respective dosing decisions for some hypothetical data scenarios. A simulation study of the operating characteristics of the model is also presented in this appendix.

16.1.1 Statistical model for triple combination

The statistical model comprises single-agent toxicity parts, which allow the incorporation of single-agent goxicity information, and interaction parts to describe two-way drug safety interactions. The proposed statistical model uses a meta-analytic framework (Spiegelhalter 2004, Neuenschwander 2016) to combine all historical and concurrent data.

16.1.1.1 Single agent parts

Let $\pi_i(d_i)$ be the risk of DLT for a compound i given as a single agent dose at dose d_i (i=1,2,3) The single agent dose-DLT models are logistic:

$\text{logit}(\pi_i(d_i))=\log(\alpha_i)+\beta_i \log(d_i/d_i^*)$ i=1,2,3 (1)

where d_i^*, the reference dose, is used to scale the doses of each compound. The reference doses are defined in the appropriate model specifications sections.

Hence, α_i (>0) is the single-agent odds of a DLT at d_i^* and β_i (>0) are the increase in the log-odds of a DLT by a unit increase in log-dose.

16.1.1.2 Interaction

Under no interaction, the risk of a DLT for combination dose (d_1, d_2, d_3) is:

$\pi_{123}^0(d_1, d_2, d_3) = 1 - (1-\pi_1(d_1))(1-\pi_2(d_2))(1-\pi_3(d_3))$

To allow for interaction between each pair of compounds, odds mutlipliers, η_{12}, η_{13}, η_{23}, are introduced.

The risk of DLT for combination dose (d_1, d_2, d_3) is then given by:

$\text{odds}(\pi_{123}(d_1, d_2, d_3))=\exp[\eta_{12}(d_1d_2/ d_1^* d_2^*) + \eta_{13}(d_1d_3/ d_1^* d_3^*) + \eta_{23}(d_2d_3/ d_2^* d_3^*)]*\text{odds}(\pi_{123}^0(d_1,d_2,d_3))$

where,

$\text{odds}(\pi) = \pi/ (1-\pi)$;

η_{ij} is the log of the odds ratio between the interaction and no interaction model at dose d_i^* and d_j^* for treatment i and j and a zero dose of the third treatment;

$\eta = \eta_{12} + \eta_{13} + \eta_{23}$ is the log of the odds ratio between the interaction and no interaction model at dose d_1^* d_2^* and d_3^* for all three treatments. Here $\eta=0$ corresponds to no overall interaction with $\eta>0$ and $\eta<0$ representing overall synergetic and antagonistic toxicity respecvtively.

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16.1.2 Prior specifications

The Bayesian approach requires the specification of prior distributions for the model parameters log(α) and log(β).A meta-analytic framework approach was used to derive the prior distribution for these model parameters.

16.1.2.1 Prior distributions for the logistic parameters

16.1.2.1.1 Description of the meta-analytic framework approach

The aim of this approach is to derive prior distribution for the logistic parameters (log (α^*), log (β^*)) of the new trial using DLT data from historical studies.

Let r_{ds} and n_{ds} be the number of participants with a DLT, and the total number of participants at dose d in historical trial s (s=1,…,S). The corresponding probability of a DLT is π_{ds}. The model specifications for the derivation of the prior are as follows:

$$rd_s \mid \pi d_s \sim Bin\ (\pi d_s, nd_s)$$

$$logit\ (\pi_{ds}) = log(\alpha_s) + \beta_s\ log(d/d^*)$$

$$(log(\alpha_s), log(\beta_s)) \mid \mu, \psi \sim BVN(\mu, \psi),\ s=1,\ldots,S$$

$$(log(\alpha^*), log(\beta^*)) \mid \mu, \psi \sim BVN(\mu, \psi)$$

The parameters $\mu = (\mu_1, \mu_2)$ and ψ are the mean and between-trial covariance matrix for the logistic parameters, the latter with standard deviations τ_1, τ_2, and correlation ρ. The parameters τ_1 and τ_2 quantify the degree of between trial heterogeneity. The following priors will be used for these parameters:

- normal priors for μ_1 and μ_2,
- log-normal priors for τ_1 and τ_2, and
- a uniform prior for ρ

The prior for model parameters in the new trial, (log(α*),log(β*)), is the predictive distribution:

$$(log(\alpha^*), log(\beta^*)) \mid (r_{ds}, n_{ds} \quad s=1,\ldots,S)$$

Since the predictive distribution is not available analytically, Markov chain Monte Carlo (MCMC) is used to simulate values from this distribution. This is implemented using JAGS version 3.12. The sample from this distribution is then approximated by a mixture of bivariate normal (BVN) distributions. BVN mixtures with increasing numbers of mixture components are fitted to the sample using the expectation-maximization (EM) algorithm (Dempster 1977). The optimal number of components of the mixture is then identified using the Akaike information criterion (AIC) (Akaike 1974).

16.1.2.1.2 Prior specification

Single agent components

Weakly informative priors are assumed for log(α) and log(β), with mean (μ1) equal to logit (0.10) corresponding to the anticipated DLT rate at the reference dose (d_1^*=sabatolimab 800 mg, d2*=azacitidine 75 mg/m^2, d_3^*=venetoclax 400 mg)) and with mean (μ2) equal to 0

[redacted]

corresponding to a dose leading to a doubling in the odds of the risk of a DLT. Priors for τ_1 and τ_2 are assigned such that (1) their medians correspond to substantial between trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between trial standard deviations (Neueuschwander 2014).

Interaction components

Because of no-drug interactions observed so far in clinical studies in patients treated with sabatolimab and azacitidine or treated with venetoclax and azacitidine and no drug-drug interactions expected between sabatolimab and venetoclax, a prior centered on an assumption of no interaction but with appropriate uncertainty that allows for both synergistic and antagonistic toxicity was considered for each 2-by-2 drug interactions.

The prior distributions for the model used for deriving the meta-analytic priors are specified in Table 16-1 below.

Table 16-1 Prior distributions for single-agent and interactionparameters

Parameter	Prior distribution
Intercept and slope for each single-agent component	
• μ_1	N(mean = logit(0.10), sd = 2)
• μ_2	N(mean = 0, sd=1)
• τ_1	log-normal(mean = 0.5, sd = log(4)/1.96)
• τ_2	log-normal(mean = 0.25, sd = log(4)/1.96)
• ρ	uniform (-1,1)
• Probabilities of exchangeability	1
Slope for each 2-by-2 interaction term	
• μ	N(mean = 0, sd=0.5)
• τ	log-normal(mean - log(0.125), sd= log(4)/1.96)
• Probability of exchangeability	0.9

16.1.2.1.3 Historical data

The prior described above was then updated by using the dose-DLT data from a Novartis study [PDR001X2105] in participants treated with sabatolimab in combination with azacitidine (arm 6b) as well an external study (Wei et al (2019)). Historical data are presented in Table 16-2 and Table 16-3.

Table 16-2 Historical data from [PDR001X2105 (arm 6b)] for sabatolimab in combination with azacitidine

Sabatolimab dose level (mg)	Number of enrolled participants	Number of participants for DDS	Number of participants with a DLT
400 mg Q2W	6	6	0
400 mg Q2W	9	9	0
240 mg Q2W	6	4	0

[redacted]

Sabatolimab dose level (mg)	Number of enrolled participants	Number of participants for DDS	Number of participants with a DLT
800 mg Q4W	5	5	0

Table 16-3 Historical data from [Wei et al (2019)] for venetoclax and azacitidine]

Azacitidine or Venetoclax dose level	Number of participants enrolled	participants evaluable for DDS	Number of participants with a DLT
Azacitidine (75 mg/m2 Day 1- 7)	2	2	0
Azacitidine (75 mg/m2 Day 1- 7) + Venetoclax (400 mg D1 -28)	5	5	1

16.1.2.2 Summary of prior distributions

The prior distributions of the model parameters are summarized in Table 16-4.

The prior summaries for DLT rates are summarized in Table 16-5.

Table 16-4 Prior distribution (BVN Mixture (log(α, β))

Parameter	**Mean**	**Standard deviations**
Single agent sabatolimab (μ_1, μ_2)	(-4.059 ; 0.03786)	(1.402 ; 0.9895)
Single agent azacitidine (μ1, μ2)	(-4.085 ; 0.00547	(1.356 ; 1.018)
Single agent venetoclax (μ1, μ2)	(-2.287 ; 0.00427)	(1.494 ; 0.9826)
Interaction sabtolimab-azacitidine (μ)	-0.199353	0.4931
Interaction azacitidine-venetoclax (μ)	-0.003551	0.5091
Interaction azacitidine-venetoclax (μ)	0.014003	0.4839

Table 16-5 Summary of posterior distributions

Sabatolimab Q4W dose (mg)*	**Prior probabilities that p(DLT) is in the interval:**					**Quantiles**		
	[0,16)	**[0,16,0.33)**	**[0.33,1]**	**Mean**	**SD**	**2.5%**	**50%**	**97.5%**
400	0.506	0.277	0.217	0.218	0.192	0.017	0.158	0.752
800	0.492	0.262	0.246	0.232	0.210	0.014	0.164	0.805

* in combination with fixed dose of Venetoclax and Azacitidine.

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16.1.3 Hypothetical on-study scenarios

To illustrate the performance of the Bayesian model used to guide the tolerability assessment in the Safety run-in part for sabatolimab in combination with venetoclax plus azacitidine, hypothetical data scenarios are displayed in Table 16-6 below. Decision might be based on additional safety, pharmacokinetic and pharmacodynamic information.

The study will continue if probability of excessive toxicity (i.e. DLT rate ≥ 33% i.e. excessive toxicity) every dose level is less than 0.25, satisfying the EWOC criteria. In addition, the probability of excessive toxicity for newly participants is provided.

Table 16-6 Probability of excessive toxicity estimated by the Bayesian model after each cohort

Scenario	Cohort of safety run-in part	Sabatolimab Q4W dose (mg)**	Number of		Dose level		
			Evaluable participants	DLTs*	Sabatolimab dose	Median P(DLT)	P (excessive toxicity)
1	Cohort 1	400	3	0	400	0.090	0.058
2	Cohort 1	400	3	1	400	0.193	0.262
3	Cohort 1	400	4	0	400	0.082	0.039
4	Cohort 1	400	4	1	400	0.167	0.182
5	Cohort 1	400	5	0	400	0.076	0.028
6	Cohort 1	400	5	1	400	0.150	0.128
7	Cohort 1	400	5	2	400	0.257	0.377
8	Cohort 1	400	6	0	400	0.071	0.016
9	Cohort 1	400	6	1	400	0.142	0.097
10	Cohort 1	400	6	2	400	0.233	0.298
11	Cohort 1	400	3	0			
	Cohort 2	800	9	0	800	0.049	0.002
12	Cohort 1	400	3	0			

	Cohort 2	800	9	1	800	0.094	0.015
13	Cohort 1	400	3	0			
	Cohort 2	800	9	2	800	0.153	0.068
14	Cohort 1	400	3	0			
	Cohort 2	800	9	3	800	0.222	0.208
15	Cohort 1	400	3	1			
	Cohort 2	800	9	0	800	0.085	0.010
16	Cohort 1	400	3	1			
	Cohort 2	800	9	1	800	0.143	0.060
17	Cohort 1	400	3	1			
	Cohort 2	800	9	2	800	0.206	0.173
18	Cohort 1	400	3	1			
	Cohort 2	800	9	3	800	0.277	0.376
19	Cohort 1	400	4	1			
	Cohort 2	800	9	0	800	0.08	0.009
20	Cohort 1	400	4	1			
	Cohort 2	800	9	1	800	0.136	0.050
21	Cohort 1	400	4	1			
	Cohort 2	800	9	2	800	0.196	0.154
22	Cohort 1	400	4	1			
	Cohort 2	800	9	3	800	0.264	0.331

* Number of participants with at least one DLT.
**In combination with fixed dose of Venetoclax and Azacitidine

Dose level Sabatolimab 400 mg Q4W:

[redacted]

If one DLT with 3 evaluable participants, the probability of excessive toxicity (i.e. DLT rate of >= 33%) with dosing regimens of sabatolimab 400 mg is >= 25% not satisfying the EOWC criteria. In this case, it would be recommended to stop the trial.

If more than 1 DLT with 4,5,6 evaluable participants, the probability of excessive toxicity (i.e. DLT rate of >= 33%) with dosing regimens of sabatolimab 400 mg is >= 25% not satisfying the EOWC criteria. In this case, it would be recommended to stop the trial.

Dose level Sabatolimab 800 mg Q4W:

- **In case of no DLT in the first cohort (sabatolimab 400 mg Q4W:**
  - If <=3 DLTs out of 9 evaluable participants are observed in the second cohort, the probability of excessive toxicity (i.e. DLT rate of >= 33%) with dosing regimens of sabatolimab 800 mg is < 25% satisfying the EOWC criteria. In this case, it would be recommended to start expansion part.
  - If 4 or more DLT out of 9 evaluable participants are observed in the second cohort, the probability of excessive toxicity (i.e. DLT rate of >= 33%) with dosing regimens of sabatolimab 800 mg does not satisfy the EOWC criteria. In this case, it would be recommended to stop the trial.
- **In case of 1 DLT out of 4 evaluable participants in the first cohort (sabatolimab 400 mg Q4W)**
  - If <= 2 DLTs out of 9 evaluable participants are observed in the second cohort, the probability of excessive toxicity (i.e. DLT rate of >= 33%) with dosing regimens of sabatolimab 800 mg is < 25% satisfying the EOWC criteria. In this case, it would be recommended to start expansion part
  - If >=3 DLTs out of 9 evaluable participants are observed in the second cohort, the probability of excessive toxicity (i.e. DLT rate of >= 33%) with dosing regimens of sabatolimab 800 mg does not satisfy the EOWC criteria. In this case, it would be recommended to stop the trial.

16.1.4 Operating characteristics

16.1.4.1 Scenarios

In order to show how the design performs, six hypothetical scenarios are investigated:

- Scenario 1 (prior toxicity): the true DLT rate in both cohorts (Sabatolimab 400 and 800 mg Q4W) are similar to prior information; the combination of sabatolimab in combination with venetoclax and azacitidine is safe whatever the dose of sabatolimab tested.
- Scenario 2 (low toxicity with dose-DLT slope): the true DLT rate in first cohort is equal to 10% (defined as safe) and the true DLT rate in the second cohort is equal to 20% (defined as safe).
- Scenario 3 (threshold toxicity): the true DLT rate in both cohorts are equal to 33% (threshold to declare an excessive toxicity) without a dose-DLT relationship.
- Scenario 4 (high toxicity without dose-DLT slope): The true DLT rate in both cohorts are equal to 40% (defined as an excessive toxicity) without a dose-DLT relationship.

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- Scenario 5 (high toxicity with dose-DLT slope): The true DLT rate in first cohort is equal to 20% (defined as safe) and the true DLT rate in the second cohort is equal to 40% (defined as an excessive toxicity).
- Scenario 6 (very high toxicity with dose-DLT slope): The true DLT rate in first cohort is equal to 25% (defined as safe) and the true DLT rate in the second cohort is equal to 50% (defined as an excessive toxicity).

16.1.4.2 Simulation results

Metrics to assess the operating characteristics

Operating characteristics are reviewed based on the simulation results under the six scenarios. The metrics reviewed are:

- True DLT rate in the first cohort
- True DLT rate in the second cohort
- Probability of excessive toxicity after the first cohort.
- Probability of excessive toxicity after the second cohort.
- Probability of excessive toxicity in at least one cohort.
- Average sample size for the safety run-in part.

Operating characteristics

Table 16-7 presents the probability to declare an excessive toxicity (i.e. the number of simulations for which the probability that the true DLT rate is ≥ 33% is equal or higher than 25% for the different scenarios mentioned above.

Table 16-7 Operating characteristics for different true values of DLT rate

Scenario	True DLT rate in the first cohort	True DLT rate in the second cohort	Patients receiving an overdose	probability to stop	average sample size of safety run-in part
1 (prior toxicity)	21.8%	23.2%	0	42%	12
2 (low toxicity with dose-DLT slope)	10%	20%	0	19%	14
3 (Threshold toxicity)	33%	33%	100%	70%	9
4 (high toxicity without dose-DLT slope)	40%	40%	100%	84%	8
5 (high toxicity with dose-DLT slope)	20%	40%	51%	59%	12
6 (very high toxicity with dose-DLT slope)	25%	50%	43%	75%	10

Simulation performed in R3.6.1 with number of simulation =1000 and randomization seed 453453 First cohort size of 3, 4, 5, 6 participants and second cohort size of 9, 10, 11 or 12 participants were considered for the simulation.

16.1.5 References

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16.2 Appendix 2: Concomitant medications to be used with caution and/or requiring action

The following lists are not comprehensive and are only meant to be used as a guide. The lists are based on the Novartis Internal Oncology Clinical Pharmacology Guidance, Drug-Drug Interaction and Co-Medication Considerations (v05, release date: 2015), which was compiled from the Indiana University School of Medicine's P450 Drug Interaction Table (medicine.iupui.edu/clinpharm/ddis/main- table/) and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies –Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012) (fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf), and the University of Washington's Drug Interaction Database (druginteractioninfo.org/).

Please refer to Section 6.2.1.1 for actions that need to be taken when using these concomitant medications. Please contact the Novartis medical monitor with any questions.

Table 16-8 List of medications to be used with caution and/or requiring action during study drug treatment

Strong inhibitors of CYP3A	ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak), indinavir/ritonavir, tipranavir/ritonavir, ritonavir, cobicistat, indinavir, ketoconazole, troleandomycin, telaprevir, danoprevir/ritonavir, elvitegravir/ritonavir, saquinavir/ritonavir, lopinavir/ritonavir, itraconazole, voriconazole, mibefradil, clarithromycin, posaconazole, telithromycin, grapefruit juice[1], conivaptan, nefazodone, nelfinavir, idelalisib, boceprevir, atazanavir/ritonavir, darunavir/ritonavir
Moderate inhibitors of CYP3A	aprepitant, amprenavir, atazanavir, cimetidine, ciprofloxacin, crizotinib, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, faldaprevir, fluconazole, grapefruit juice[1], imatinib, isavuconazole, netupitant, nilotinib, tofisopam, *Schisandra sphenanthera* (nan wu wei zi), asafoetida resin (*Ferula asafoetida*), verapamil
Strong inducers of CYP3A	carbamazepine, enzalutamide, lumacaftor, phenobarbital, phenytoin, rifabutin, rifampicin, mitotane, St. John's wort (*Hypericum perforatum*)

Moderate inducers of CYP3A	bosentan, dabrafenib, efavirenz, etravirine, genistein, modafinil, nafcillin, tipranavir/ritonavir, lopinavir, telotristat, thioridazine
Inhibitors of P-gp	alogliptin, amiodarone, azithromycin, canaglifozin, captopril, carvedilol, clarithromycin, clopidrogel, conivaptan, cremophor EL and RH40, curcumin, daclatasvir, diltiazem, dronedarone, eliglustat, erythromycin, felodipine, fluvoxamine, fostamatinib, ginkgo (Ginkgo biloba), green tea, indinavir, isavuconazole, itraconazole, ivacaftor, ketoconazole, lapatinib, lopinavir, mibefradil, milk thistle (silymarin, silibinin), mirabegron, nelfinavir, nifedipine, nitrendipine, ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak), paroxetine, propafenone, quercetin, quinidine, quinine, ranolazine, rifampicin, ritonavir, rolapitant, saquinavir, Schisandra chinensis extract (wuweizi), simeprevir, St. John's wort extract (Hypericum perforatum) , survorexant, talinolol, telaprevir, telmisartan, ticagrelor, tipranavir, tolvaptan, valspodar, vandetanib, velpatasvir, verapamil, voclosporin, vorapaxar
NTI substrates of P-gp	cyclosporine, digoxin, fentanyl, paclitaxel, phenytoin, quinidine, sirolimus, tacrolimus
Substrates of P-gp (≥2X AUC change)	aliskiren, ambrisentan, atorvastatin, azithromycin, colchicine, dabigatran, digoxin, docetaxel, domperidone, doxorubicin, fentanyl, fexofenadine, lapatinib, linezolid, loperamide, maraviroc, nadolol, nevirapine, paclitaxel, proguanil, quinidine, ranolazine, ritonavir, saquinavir, simvastatin, sirolimus, sofosbuvir, tacrolimus, ticagrelor, topotecan
Substrates of P-gp mentioned in USPI	afatinib, alfuzosin, aliskiren, alogliptin, ambrisentan, apixaban, apremilast, aprepitant, boceprevir, bosentan, carvedilol, carvedilol, caspofungin, ceritinib, citalopram, colchicine, cyclosporine,

[redacted]

	dabigatran, digoxin, doxepin, doxorubicin, eribulin, everolimus, fidaxomicin, fluvastatin, fosamprenavir, gatifloxacin, idelalisib, iloperidone, indacaterol, irbesartan, lacosamide, lapatinib, levetiracetam, levofloxacin, linagliptin, losartan, maraviroc, mirabegron, moxifloxacin, naloxegol, nateglinide, nintedanib, olodaterol, pantoprazole, paroxetine, pazopanib, posaconazole, pravastatin, quinine, ranolazine, riociguat, risperidone, rivaroxaban, saquinavir, silodosin, simeprevir, sirolimus, sitagliptin, sorafenib, telaprevir, tenofovir, ticagrelor, tipranavir, tolvaptan, topotecan, umeclidinium, valsartan, vardenafil, vincristine, voriconazole
Substrates of BCRP	Atorvastatin, daunorubicin, dolutegravir, doxorubicin, hematoporphyrin, imatinib, methotrexate, mitoxantrone, paritaprevir, pitavastatin, rosuvastatin, irinotecan, ethinyl estradiol, simvastatin, sofosbuvir, sulfasalazine, tenofovir, topotecan, venetoclax

[1] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent.

[redacted]