NOVARTIS

Clinical Development

MBG453/Sabatolimab

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

Statistical Analysis Plan (SAP)

Author:	Statistician, [redacted]; Statistician, [redacted]

Document type:	SAP Documentation
Document status:	Amendment 2
Release date:	06-June-2023
Number of pages:	46

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
17-May-2021	FPFV	Creation of first version	NA First version (based on protocol v00 from 07-Dec-20)	NA
17-Jan-2023	Prior to final CSR DBL	Update to align with protocol amendment 1 and 2, and lean the final CSR due to the recruitment halt after the completion of safety run-in part.	Amendment 1 (based on protocol amendment 2 from 06-Oct-2021)	-Change the term “subject” to “participant” throughout the SAP. - Change the term referring to sabatolimab from “study drug” to “investigational drug”. -Section 2.2.5, subgroup analysis removed. -Section 2.5.2.2, CR primary analysis removed. -Section 2.6.1.2, - Update the definition of time-to-event endpoints; General sentence about the production of K-M outputs added -Section 2.6.5, analysis of fatigue removed. - [redacted]
6-Jun-2023	Prior to final DBL	Update per program-level standard for safety, review of dry-run and PK dry-run discussion	Amendment 2 (updates on PK and IG analyses, definition of vital sign population and last exposure to study treatment)	Section 2.5.1.1, Summary table of DLTs added. Section 2.6.3.1, Exclude the concentration at EOT, 30-day safety follow-up and 150-day safety follow-up visit from the sabatolimab PK concentration summary table and graph; For the summary table of venetoclax PK concentration, only display the patients whose prior dose was 400 mg; Drug-drug interactions analysis removed. Section 2.6.4, Analysis for ADA status updated. Section 2.6.2.7, Population for vital sign summary updated Section 4, Calculations of dates of last exposure to study treatment updated

Table of contents

List of tables

List of figures

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
AST	Aspartate Aminotransferase
AUC	Area under the curve
BMA	Bone marrow aspirate
BMI	Body Mass Index
BSA	Body surface area
BUN	Blood Urea Nitrogen
CK	Creatinine Kinase
COVID-19	Coronavirus disease 2019
CR	Complete remission
CRF	Case Report/Record Form (paper or electronic)
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
DDS	Dose Determining Set
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EFS	Event-free survival
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
ePRO	Electronic Patient Reported Outcome
[redacted]	[redacted]
eSAE	Electronic Serious Adverse Event
eSource	Electronic Source
EWOC	Escalation with overdose control
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy- Fatigue
FAS	Full Analysis Set
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
IG	Immunogenicity
INR	International Normalized Ratio
IPSS-R	Revised International Prognostic Scoring System
IRT	Interactive Response Technology
IWG	International Working Group
LDH	lactate dehydrogenase
LFS	Leukemia-free survival
mCR	Marrow complete remission
MDS	Myelodysplastic syndromes
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MPN	Myeloproliferative neoplasm
MRD	Measurable residual disease
NCI	National Cancer Institute
NGS	Next Generation Sequencing
ORR	Overall response rate
OS	Overall survival
PAS	Pharmacokinetic Analysis Set
PD	Progressive Disease
PFS	Progression-free survival
[redacted]	[redacted]
[redacted]	[redacted]
PK	Pharmacokinetic(s)
PR	Partial Remission
PRO	Patient Reported Outcomes
Q4W	every 4 weeks
QTcF	QT interval corrected by Fridericia's formula
[redacted]	[redacted]
RBC	red blood cell(s)
[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
[redacted]	[redacted]
TSH	Thyroid-Stimulating Hormone
WBC	white blood cell(s)
WoC	Withdrawal of study Consent

1 Introduction

This statistical analysis plan (SAP) describes the planned analyses for the Clinical Study Report (CSR) of the study MBG453B12203, a 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 myelodysplastic syndrome (MDS) as per IPSS-R criteria.

The content of this SAP is based on the MBG453B12203 protocol including amendment 2 (06-Oct-2021). All decisions regarding the analysis, as defined in the SAP document, have been made prior to database lock (DBL).

As specified in the section 12.7 of the study protocol, safety meetings were conducted during the safety run-in part of the study to assess the tolerability of sabatolimab at two different doses (400 mg and 800 mg administered every 4 weeks) when given together with azacitidine and venetoclax before enrolling participants in the expansion part of the study. The second safety review meeting was held on 26-Sep-2022. The investigators and steering committee members agreed that there was no new safety concern identified with the combination of sabatolimab 800mg Q4W, azacitidine 75mg/m2 for 7days out of a 28-day cycle, venetoclax 400 mg QD for 14 days and that the expansion phase (Part 2) could be opened for enrollment of participants.

However, Novartis decided to permanently halt the recruitment of new participants into study MBG453B12203 in September 2022 (recruitment halt letter sent to investigators on 27-Sep-2022). As a result, the expansion part of the study will not be opened. This decision was not based on any safety findings or safety concerns with sabatolimab or the triplet combination but rather it was a Novartis strategic consideration. The decision about recruitment halt was not reflected in a protocol amendment but will be documented in the Early Termination Plan for the study. The study data will be analyzed and reported based on all available data up to DBL in an abbreviated final Clinical Study Report (CSR).

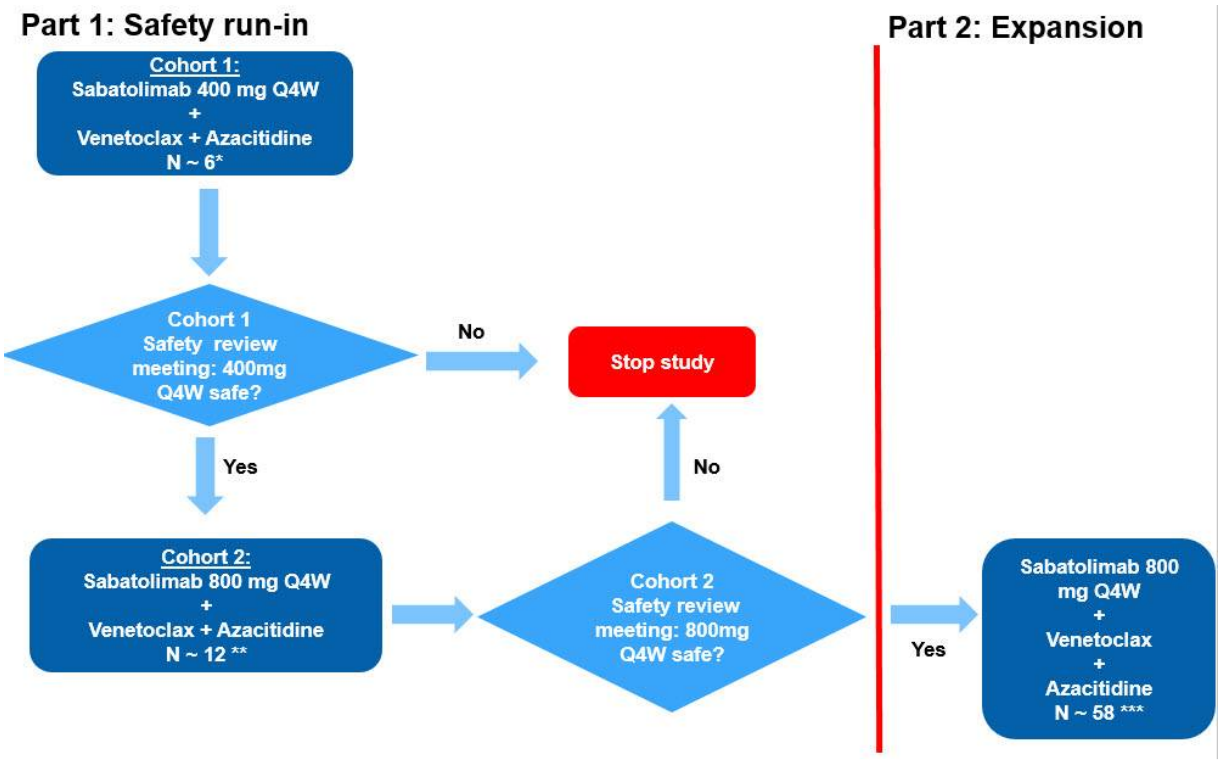
1.1 Study design

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 1-1 below. The study will enroll a total of approximately 76 participants and will be conducted in two sequential parts:

- **Part 1:** The safety run-in consists of two subsequent cohorts of 400 mg Q4W (cohort 1) and 800 mg Q4W (cohort 2) of sabatolimab in combination with a 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.
- **Part 2:** If the review of safety data from participants enrolled in cohort 2 of part I 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 stopped. 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. 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. 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, and a Safety Review Meeting has been conducted. If no safety concerns are identified at either dose level, 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.

Figure 1-1 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

1.2 Study objectives and endpoints

The objectives and associated endpoints are presented in Table 1-1 below. Due to the recruitment halt for the expansion part after the safety run-in,the evaluation of the changes from baseline in fatigue (only for Part 2) [redacted] will not be analyzed for the abbreviated CSR. All other objectives and endpoints will be presented.

Table 1-1 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 dose limiting toxicities (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 follows: 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.
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).
• To assess the improvement in RBC/platelets transfusion independence	• Proportion of participants who are RBC/platelets transfusion independent and duration of transfusion independence 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

Objective(s)	Endpoint(s)
	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 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 Cheson 2006 criteria) as per investigator assessment.	• 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 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

Objective(s)	Endpoint(s)
	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]	

2 Statistical methods

2.1 Data analysis / general information

The primary analysis, as well as the analyses that will be used for the safety review meetings of the safety run-in part of the study will be performed by Novartis. SAS or R will be used to perform all data analyses and to generate tables, figures and listings.

As Novartis decided to halt enrollment of the expansion part of the study in September 2022, the study data will be analyzed and reported based on all data up to DBL in an abbreviated final Clinical Study Report (CSR).

Data included in the analysis / data cut-off handling

For each of the safety review meetings a data cut-off date will be established after the targeted number of evaluable participants have completed 2 cycles of treatment. All safety data (including duration of exposure to study drugs, dose interruptions/reductions, study drug discontinuation, etc.), demographics, disease history, hematology data, blast counts from bone marrow and PK data with an assessment date or event start date (e.g. laboratory assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. The list of analyses to be presented at the time of the safety review meetings are provided in Section 2.8.

For the abbreviated CSR, all data collected prior to DBL will be included in the analysis.

General analysis conventions

Qualitative data (e.g. gender, race) will be summarized by means of contingency tables; a missing category will be included as applicable. Percentages will be calculated using the number of participants in the relevant population or subgroup as the denominator.

Quantitative data (e.g. age, body weight) will be summarized by appropriate descriptive statistics (e.g. mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum).

2.1.1 General definitions

"Investigational drug" refers to sabatolimab

"Study treatment component*"* refers to sabatolimab or azacitidine or venetoclax.

"*Study treatment"* will refer to the combination of sabatolimab with azacitidine and venetoclax.

Other general definitions are detailed in Appendix Section 4.

2.2 Analysis sets

For the safety review meetings, the analysis sets defined below will be restricted to the population enrolled in the safety run-in part and participants will be analyzed according to the dose regimen they have been assigned to: sabatolimab 400 mg Q4W for the first cohort and sabatolimab 800 mg Q4W for the second cohort. At the time of the second Safety Review meeting to assess the over toxicity risk for the second cohort (800 mg Q4W dose level), the available data from the first cohort (400 mg Q4W dose level) will also be displayed.

For analysis in the abbreviated CSR, the analysis sets defined below will include all participants from the safety run-in part. Participants will be analyzed according to the dose regimen they have been assigned to (sabatolimab 400 mg or 800 mg Q4W columns) and overall ("All participants" column), unless otherwise specified.

2.2.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all participants who received at least one dose of study treatment. If a participant was assigned to a specific cohort without any administration of sabatolimab, but received venetoclax or azacitidine, the participant will be included in the analysis.

2.2.2 Safety Set

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

2.2.3 Dose-Determining Set

The Dose Determining Set (DDS) includes all participants from the FAS enrolled in 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 two cycles.

A participant has met the minimum exposure criterion if the participant 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 2 cycles 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.

2.2.4 Pharmacokinetic Analysis Sets

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.
- For pre-dose samples of venetoclax: patient does not vomit within 4 hours of venetoclax administration of the previous dose.

2.2.4.1 Participant Classification

Participants may be excluded from the analysis populations defined above based on the protocol deviations entered in the database and/or on specific participant classification rules defined in Table 2-1

Table 2-1 Participant classification based on protocol deviations and non protocol deviations criteria

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
FAS	No written informed consent for participation in the study	No dose of any component of study treatment
Safety Set	No written informed consent for participation in the study	No dose of any component of study treatment
DDS	No written informed consent for participation in the study	Not met the minimum exposure criterion or no sufficient safety evaluations in the absence of DLT during the DLT evaluation period
Sabatolimab-PK analysis set	No written informed consent for participation in the study	See definition of PK analysis sets
Venetoclax-PK analysis set	No written informed consent for participation in the study	See definition of PK analysis sets

2.2.4.2 Withdrawal of Informed Consent

Any data collected in the clinical database after a participant withdraws informed consent from all further participation in the study will not be included in the analyses. The date on which a participant withdraws consent is recorded in the eCRF. Additional data for which there is a separate informed consent, e.g. biological sample etc., collected in the clinical database without having obtained that consent or after withdrawal of consent will not be included in the analyses.

2.2.5 Subgroup of interest

No subgroup analysis will be conducted for the abbreviated CSR.

2.3 Patient disposition, demographics and other baseline characteristics

The FAS will be used for the analyses below. Patient disposition, demographics and other baseline characteristics will be summarized by dose level of sabatolimab (400 mg Q4W, 800 mg Q4W) and for all participants (“All participants” column).

2.3.1 Patient disposition

Number (%) of participants screened and enrolled will be summarized by country and center. For participants who did not complete screening, the reasons for not completing screening will be summarized based on "Screening Phase Disposition" eCRF.

The number (%) of participants in the FAS who started treatment, are still on treatment, who entered and discontinued post-treatment follow-up and who discontinued the study after survival follow-up will be summarized together with the respective reasons for treatment/post-treatment follow-up/end of study discontinuation (which corresponds to end of survival follow-up). All disposition information will be listed.

Protocol deviation

The number (%) of participants in the FAS with any protocol deviation will be tabulated by deviation category. All protocol deviations will be listed.

In addition to the pre-defined standard protocol deviation terms, Novartis has also defined new protocol deviations and the corresponding relationship to the COVID-19 pandemic. The protocol deviations related to the COVID-19 pandemic will be summarized by relationship category.

2.3.2 Demographics and other baseline characteristics

BMI (kg/m2) at baseline will be calculated as weight[kg] / (height[m]^2) using weight at baseline and height at screening. Body Surface Area (BSA) is based on the Mosteller formula described in Section 2.4.1.

Details on MDS diagnosis (initial diagnosis, IPSS-R risk category including the components (blasts in BM, number of cytopenias and cytogenetic abnormalities), WHO classification, current disease status (de novo or secondary) and cytogenetic abnormalities) will be tabulated and time since diagnosis summarized.

Medical history

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term. Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable outputs.

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

The Safety set will be used for the analyses below and summary tables will be presented by dose level of sabatolimab (400 mg Q4W, 800 mg Q4W) and for all participants ("All participants" column).

2.4.1 Study treatment / compliance

The duration of exposure to study treatment and to each study drug (sabatolimab, azacitidine and venetoclax) as well as the actual dose intensity, relative dose intensity and doses changes will be summarized by descriptive statistics.

2.4.1.1 Duration of exposure

The duration of exposure (in months) will be summarized for study treatment (combination) and for each study drug individually (sabatolimab, azacitidine and venetoclax) based on summary statistics and categorical analyses (e.g. exposure <1 month, at least 1 month, at least 2 months etc.). Details on start and end dates used for derivations are outlined in Appendix Section 4.

2.4.1.2 Cumulative dose

For sabatolimab, the actual cumulative dose in mg is the sum of "dose administered" from the eCRF of all cycles during the exposure to sabatolimab.

For azacitidine, the actual dose in mg/m^2 in each cycle is the "dose administered" in mg during that cycle divided by the body surface area (BSA) at the beginning of the cycle using the weight measured before the infusion at that cycle. If the weight is not collected at the beginning of the cycle, the weight from the previous visit will be considered. The actual cumulative dose in mg/m^2 is then the sum of all cycles. The following formula (Mosteller) is used for BSA:

$$BSA\ (m^2) = \sqrt{Weight\ (kg) * Height\ at\ screening\ (cm)/3600}$$

For venetoclax, the actual cumulative dose in mg is the sum of "dose administered" from the eCRF of all cycles during the exposure of venetoclax.

2.4.1.3 Dose intensity and relative dose intensity

Dose intensity is defined for participants with non-zero duration of exposure. For participants who did not take the drug, the dose intensity is by definition equal to zero. The actual dose intensity (computed as the ratio of actual cumulative dose received and duration in days from first to last cycle initiated) and the relative dose intensity (computed as the ratio of actual dose intensity and planned dose intensity) will be summarized for each study treatment component by descriptive statistics. The planned dose intensity for each of the study treatment components is the ratio of planned cumulative dose and duration in days from first to last cycle initiated:

- Sabatolimab: the planned dose intensity is 400 mg/28 days or 800 mg/28 days,
- Azacitidine: the planned dose intensity is 75 mg/m^2/day which is equivalent to 525 mg/m^2/28 days,
- Venetoclax: the planned dose intensity is 400 mg/day which is equivalent to 5600 mg/28 days when the recommended full daily dose of venetoclax is 400 mg.

The relative dose intensity is then computed as the ratio of actual dose intensity and planned dose intensity. For example, if a participant received sabatolimab at 600 mg Q4W on average throughout the study (instead of the 800 mg Q4W as planned per protocol), the relative dose intensity for this participant is 0.75.

Details on the duration in days from the first to last cycle initiated for the derivation of the dose intensity and the relative dose intensity are provided in Appendix Section 4.

2.4.1.4 Dose reduction, dose interruption and permanent discontinuations

The number (%) of participants with any dose changes (incl. reductions, interruptions, or permanent discontinuations) and the reasons (e.g. AE, dosing error, dispensing error) will be taken from the 'Study Treatment eCRF' and summarized by study treatment component. The total duration of interruptions by participant will be summarized for the study population by time intervals, e.g. < 1week, ≥ 1 -< 2 weeks, ≥ 2-< 3 week etc. (these time intervals may be adjusted depending on the observed data).

2.4.1.5 Cycle initiated

The number of cycles initiated by participant will be summarized.

2.4.2 Prior, concomitant and post therapies / HSCT

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

Prior anti-neoplastic medications will be summarized using the FAS. Medications will be summarized by ATC class and preferred term.

Anti-neoplastic medications after discontinuation of study treatment during follow-up within the study will be summarized using the FAS by ATC class and preferred term. All HSCTs will be listed.

Transfusions of blood products (including those not related to MDS) prior and after start of study treatment will be listed. Only MDS related transfusions (e.g. bleeding, surgical procedure, hemolysis, infections) of platelets and red blood cells will be summarized using the FAS. For that, the number of transfusion units will be normalized by time (i.e. fixed 8 week interval, mentioned below as episode) prior to and on-treatment. The number of participants with at least one transfusion episode, the number of transfusion episode per participant and the number of units per episode will also be described. Further analyses to summarize transfusion independence and dependence are described in the efficacy section.

2.5 Analysis of the primary objectives

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).

2.5.1 Primary endpoints and estimand

2.5.1.1 Safety run-in (Part 1)

For the Safety run-in part, the primary endpoint is the incidence of DLTs during the first 2 cycles of treatment for participants in the DDS. The number and percentage of DLTs occurring during the DLT evaluation period will be summarized by system organ class and preferred term in the DDS, and the DLTs will be listed

Details on the definition of DLT which are to be captured in the Adverse Event eCRF were defined as described in (Table 6-4 of study protocol).

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

The primary endpoint is the proportion of participants included in the FAS and assigned to sabatolimab at the 800 mg Q4W dose level (in both safety run-in and expansion parts) who achieved a complete remission (CR) as per investigator assessment.

Response assessment rules

Response assessment will be performed by the investigator according to the assessment schedule depicted in protocol Table 8-1 based on available bone marrow assessment (C3D1, C7D1, C10D1, C13D1 and then C19D1, C25D1 and then every 12 cycles), hematology data (at D1, D8, D22 of the first 2 cycles and then D1 and D8 of each cycle until end of treatment and then every 12 weeks) and all transfusions records as detailed in s using the modified version of the published response criteria IWG for MDS. Moreover, response assessments can be performed at any time if clinically indicated, e.g. for confirmation of response but also for any suspicion of progression/relapse. These assessments are recorded as an unscheduled visit in the eCRFs and will be considered for the overall determination of response and progression/relapse with the respective assessment date.

The investigator does not determine best overall response, he/she is assessing only the response based on the given bone marrow and peripheral blood data, the history of transfusions and myeloid growth factor received within the last 2 weeks.

The best overall response (BOR) will be derived based on the CR primary endpoint rules by Novartis as below:

- CR = at least one determination of CR without progression or relapse from CR within the four weeks after CR
- mCR = at least one determination of mCR (and not qualifying for a CR).
- PR = at least one determination of PR (and not qualifying for a CR, mCR).
- HI = at least one determination of HI (and not qualifying for a CR, mCR, PR)
- SD = at least one SD assessment and not qualifying for CR, mCR, PR or HI).
- PD = progression after start of treatment and not qualifying for CR, mCR, PR, HI or SD.
- UNK = all other cases (i.e., not qualifying for confirmed CR or mCR or PR or HI and without SD or progression).

Details for the definition of response categories (captured in the eCRF by the Investigator) as defined in Table 8-2 of the protocol, are described in Table 2-2 below.

Table 2-2 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:** <= 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:** [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**)**

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

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.

Primary estimand

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.

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

- **Population:** Adult participants as described by inclusion/exclusion criteria not eligible for intensive chemotherapy nor for HSCT with high or very high risk MDS (IPSS-R criteria) (Greenberg et al 2012) as per inclusion/exclusion criteria and 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 initiates 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).

- **Intercurrent events:**
  - **Study treatment modification:** all CR will be taken into account regardless of any study treatment component interruption, dose adjustment or permanent discontinuation.
  - **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). 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).

2.5.2 Statistical hypothesis, model, and method of analysis

2.5.2.1 Safety run-in (Part 1)

DLT analysis

A Bayesian model will be used to assess whether sabatolimab at the two tested dose levels is not meeting overdose criteria when added to azacitidine and venetoclax in participants from the DDS. The relationship between dose and the probability of DLT is modeled using a logistic regression model. Detail of the characteristics of this Bayesian model is provided in Appendix Section 16.1 of the protocol.

After each cohort in the safety run-in part, the posterior distribution for the risk of DLT for new participants at the dose level of interest will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT for each dose level of sabatolimab lies within the interval [33%, 100%] (i.e. excessive toxicity).

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

CR primary analysis

As Novartis decided to halt the enrollment in the expansion part, only the CR rate by the dose level of sabatolimab with exact 95% confidence interval will be reported in the abbreviated CSR.

2.5.3 Handling of missing values/censoring/discontinuations

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

For the determination of CR, only assessments after first dose of study treatment and prior to the start of any other anti-neoplastic therapy/HSCT as per investigator evaluation are considered. An adequate response assessment is considered any disease assessment indicating response status apart from “unknown” or “not done”. Participants who discontinued trial prior to the first efficacy assessment (i.e. C3D1) will be reported with best response as ‘Unknown’.

2.6 Analysis of secondary objective(s)

The secondary objectives are to assess the overall response rate (ORR), CR/mCR rate, duration of CR, 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, immunogenicity and safety.

2.6.1 Efficacy

2.6.1.1 Safety run-in (Part 1)

CR+mCR and overall response (ORR) rates

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. CR/mCR rate will be provided with exact 95% confidence interval (Clopper and Pearson 1934).

ORR rate is defined as the proportion of participants with best overall response of hematological improvement (HI) or better as per investigator assessment. ORR rate will be provided with exact 95% confidence interval (Clopper CJ and Pearson ES 1934). CR/mCR and ORR will be provided by dose level of sabatolimab.

Improvement of RBC/platelets transfusion independence

RBC/Platelets transfusion independence rate is defined as the proportion of participants having received no RBC/Platelets transfusions during at least 8 consecutive weeks after start of treatment. The number and percentage of participants will be shown for the FAS and then also in only those with transfusion dependence at baseline. Percentages will be provided with exact 95% confidence interval (Clopper and Pearson 1934). Shift tables will be provided to describe the transfusion status at baseline versus the best transfusion status postbaseline.

For participants with at least one period of transfusion independence post-baseline, the total duration of all transfusion independence periods (which all individually must be at least 8 weeks) will be also summarized. The duration of each period of transfusion independence is defined from the end date of the last transfusion received until the date transfusions are given again or last date of treatment administration in case transfusions had not (re-)started during treatment.

The total duration of all transfusion independence periods is the sum of each period of the transfusion independence. The data will be summarized by dose level of sabatolimab.

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

All time-to-event endpoints (including duration of CR, time to CR/mCR, duration of response, duration of CR/mCR, OS, EFS, PFS and LFS) will be derived and stored in analysis datasets, and the individual time and specific event / censoring type will be listed. However, the amount of available follow-up data and number of events will determine if standard KM tables and/or graphics will be produced, which will be further discussed in the TFL shell.

Bone marrow blasts percentage will be listed. In addition, for some selected laboratory parameters and for bone marrow blasts percentage, trends over time (baseline and on-treatment timepoints during the first 6 cycles of treatment including C7D1 assessment) will be displayed via boxplots, and corresponding tables displaying the summary statistics for these selected timepoints will be produced.

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. CR/mCR rate will be provided with exact 95% confidence interval (Clopper CJ and Pearson ES 1934). The same rules applied to the primary endpoint (i.e. CR rate) will be applied to the CR/mCR rate.

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. ORR rate will be provided with exact 95% confidence interval (Clopper and Pearson 1934). The same rules applied to the primary endpoint (i.e. CR rate) will be applied to CR/mCR rate.

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, 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, or death whichever occurs first. If participant did not relapse nor progress/die, the duration of response will be censored at the 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 the last adequate assessment prior to the start of that therapy, and thus any subsequent relapse/progression/death will not be considered as an event for duration of CR.

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, or death whichever occurs first. If the participant did not relapse, progress or die, the duration of CR/mCR will be censored at the last adequate response assessment. If the participant started a new antineoplastic therapy, without prior documented relapse or

progression, the duration of CR/mCR is censored at the last adequate assessment prior to the start of that therapy and thus any subsequent relapse/progression/death will not be considered as an event for duration of CR/mCR.

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.

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 an event for the duration of response. The date of the event will be the date of relapse, progression, or death whichever occurs first. If the participant did not relapse, progress or die, the duration of response will be censored at the last adequate response assessment. If the participant started a new antineoplastic therapy without prior documented relapse or progression, the duration of response is censored at the last adequate assessment prior to the start of that therapy and thus any subsequent relapse, progression, or death will not be considered as an event for duration of response.

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 the time of HSCT or initiation of new antineoplastic therapy.

For participants who did not reach CR/mCR, a). if they did not progress, die or progress to acute myeloid leukemia either, the time to CR/mCR will be censored at the last adequate response assessment; or b). if they progressed, died or the disease progressed to acute myeloid leukemia, the time to CR/mCR will be censored at the 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 maximum of first 6 months or 6 cycles (including C7D1 assessment) 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.

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

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, then PFS will be censored at the last adequate response assessment (on or before the cut-off date). Progression/relapse or death occurring after a). HSCT, b). interruptions or c). 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 an event and PFS will be censored at the 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 as defined by the criteria mentioned above, then LFS will be censored at the last bone marrow/peripheral blood assessments (on or before the cut-off date). Any of the three events (i.e. ≥ 20% blasts in bone marrow/peripheral blood, diagnosis of extramedullary acute leukemia or death) occurring 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

an event and LFS will be censored at the last adequate assessment of bone marrow and/or peripheral blood, or diagnosis of extramedullary acute leukemia prior to initiation of new antineoplastic therapy.

In case of two or more missing assessments prior to documented progression to leukemia, LFS will be censored at the last adequate assessment (bone marrow and/or hematology assessment) prior to the documentation of progression to leukemia.

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

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.

The OS censoring reason will be summarized as 'Alive' or 'Lost to follow-up'. Participants not known to have died will have the censoring reason 'Lost to follow-up' if the reason for discontinuation from study is 'Lost to follow-up' or 'Withdrawal of consent'. Otherwise, participants will have the censoring reason 'Alive'.

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

RBC/Platelets transfusion independence rate is defined as the proportion of participants having received no RBC/Platelets transfusions during at least 8 consecutive weeks after start of treatment. The number and percentage of participants will be shown for the FAS and then also in only those with transfusion dependence at baseline. Percentages will be provided with exact 95% confidence interval (Clopper and Pearson 1934). Shift tables will be provided to describe the transfusion status at baseline versus the best transfusion status postbaseline.

For participants with at least one period of transfusion independence post-baseline, the total duration of all transfusion independence periods (which all individually must be at least 8 weeks) will be also summarized. The duration of each period of transfusion independence is defined from the end date of the last transfusion received until the date transfusions are given again or last date of treatment administration in case transfusions had not (re-)started during treatment.

The total duration of all transfusion independence periods is the sum of each period of the transfusion independence.

2.6.1.3 Handling of missing values/censoring/discontinuations for PFS, LFS and EFS

For participants without PFS/EFS/LFS events, PFS/LFS/EFS are censored at the last adequate assessment (response assessment for PFS/EFS, bone marrow/hematology assessment for LFS).

This is the last response/bone marrow/hematology assessment conducted that is not considered as unknown.

An event occurring after two or more consecutive missing response assessments (not done or unknown) is censored in the analysis at the last adequate response assessment before the event date and reason for censoring then summarized as 'Event documented after two or more missing response assessments'.

An exact rule to determine whether there are two missing assessments is therefore needed. This rule will be based on the distance between the last adequate response assessment date and the event date. If the distance is larger than threshold D_2 then the analysis will assume that there are two missing assessments. This threshold D_2 is defined as two times the protocol specified interval between the response assessments plus the allowed window around the assessments. The protocol defines that response assessment has to be done at least at the time of bone marrow assessments that are to be done:

- Pre-dose on C3D1, then
- From C7D1, bone marrow assessments will be performed every 3 cycles (12 weeks) until C13D1 (C7D1, C10D1, C13D1), then
- Every 6 cycles (24 weeks) until C25D1 (C19D1 and C25D1) and thereafter every 12 cycles (48 week, visit: C37D1, C49D1 etc.) and as clinically indicated during the treatment period).
- At least every 12 months during follow-up for efficacy

As per the protocol, a window of +/- 1 week from the planned visit date is allowed for BMA procedures. During the post-treatment and survival follow-up phases, a visit window of +/- 2 weeks is allowed.

The censoring reason will be summarized as:

1. Ongoing without event
2. New anti-cancer therapy
3. Withdrew consent
4. Lost to follow-up
5. Event documented after two or more missing response assessments
6. Discontinuation due to participant/physician/guardian's decision

2.6.2 Safety

Safety analyses will be summarized for the safety set and by dose level of sabatolimab (400 mg Q4W, 800 mg Q4W) and for all participants ("All participants" column).

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, tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

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

1. Pre-treatment period: from the 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 the date of last administration of study treatment
3. Post-treatment period: any observation starting at day 31 after the 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.

2.6.2.1 Adverse events (AEs)

AE summaries will include all AEs occurring during on-treatment period (until 30 days after last administration of study treatment). When specified, some AEs summaries will include all AEs occurring during the overall safety period.

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 AEs will be summarized by primary system organ class, preferred term and maximum severity (based on CTCAE grades).

All AEs reported in the AE eCRF page will be listed along with the information collected on those AEs, e.g. toxicity grade, relationship to study treatment, outcome, action taken etc. AEs that started during the pre-treatment, post-treatment and after the overall safety period will be flagged in listings.

AEs will be summarized by number and percentage of participants having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT). A participant with multiple occurrences of an AE will be counted only once in the respective AE category. A participant with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

In the AE summaries, the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency in the sabatolimab 800 mg Q4W. The summaries will show 'All grades' (including AEs with missing grade) and 'Grades ≥ 3'.

The following adverse event summaries will be produced selecting all or a subset of AEs depending on seriousness, relationship to study treatment, outcome or action taken:

- AEs (all AEs (by SOC and by PT) and separately those considered related to study treatment
- SAEs and separately those considered related to study treatment
- SAEs with number of occurrences (an occurrence is defined as > 1 day between start and prior end date of record of same preferred term).
- Non-SAEs

- SAEs with fatal outcome and separately those considered related to study treatment
- AEs leading to study treatment or sabatolimab discontinuation
- Related to study treatment AEs leading to study treatment discontinuation
- AEs leading to dose adjustment/interruption for sabatolimab,venetoclax or azacitidine
- AEs requiring additional therapy
- COVID-19 related adverse events by MedDRA COVID-19 (SMQ) terms.

In addition, all AEs and SAE by SOC and PT will be also provided for the overall safety period. Adverse events for the safety follow up period (day 31-150 after last dose of sabatolimab) will be described by system organ class and preferred term.

Separate summaries for on-treatment and all deaths (including post-treatment deaths not in the AE CRF but in the survival CRF) will be produced showing reason for deaths by SOC and preferred term. All AEs, deaths, and serious adverse events (including those from the pre- and post-treatment periods) will be listed and those collected during the pre-treatment, posttreatment and overall safety period will be flagged in listings. A separate listing of deaths prior to starting treatment will be provided for all screened participants.

2.6.2.2 Adverse events of special interest / grouping of AEs

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to compound sabatolimab. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. These searches will be defined in the eCRS (electronic Case Retrieval Strategy) in the DMS (Document Management System) and a listing of search terms will be provided in the CSR.

For each specified AESI, the number (%) of participants with at least one event of the AESI occurring during on treatment period will be summarized together with the individual preferred terms in that grouping. In addition, number (%) of participants with at least one AESIs by maximum CTC grade, related AESIs, serious AESIs as well as action taken and outcome of the respective AESI will be summarized.

2.6.2.3 Deaths

Separate summaries for on-treatment and all deaths (including post-treatment deaths not in the AE CRF but in the survival CRF) will be produced showing reasons for deaths by the primary reason and PT. All deaths will be listed, post treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened participants.

2.6.2.4 Laboratory data

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.

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

Liver function parameters of interest are total bilirubin, ALT, AST and alkaline phosphatase. The number (%) of participants with the worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized.

All CTCAE grade 3 or 4 laboratory toxicities will be listed.

2.6.2.5 Other safety data

Safety data listed in this section will be analyzed and summarized for the safety set and presented by dose level of sabatolimab (400 mg Q4W, 800 mg Q4W) and for all participants ("All participants" column), and by visit/sampling time point.

2.6.2.6 ECG and cardiac imaging data

ECGs are collected as 12-lead triplicate using the ECG machines supplied by the central laboratory and then transmitted electronically to the central laboratory for central review by an independent reviewer. These central ECGs are done at screening, C1D1 pre-dose, C1D8 post-dose, C3D8 post-dose and at end of treatment; however, additional ECGs can be done if clinically indicated.

Notable ECG values during on-treatment period in participants with normal values at baseline (for the respective QTc value) will be summarized using the following criteria:

Table 2-3 Notable ECG values

ECG parameter (unit)	Clinically notable criteria
QTcF (ms)	Increase >30 and <=60 ms Increase >60 ms New >450 to <=480 ms New >480 to <=500 ms New >500 ms
HR (bpm)	Increase >25% and HR >100 bpm Decrease >25% and HR<50 bpm
PR (ms)	Increase from baseline >25% and to a value > 200 ms New value of > 200 ms
QRS (ms)	Increase from baseline >25% and to a value > 120 ms New values of QRS > 120 ms

In addition, local ECGs are performed but not used for summary of QTc values. If abnormalities are observed based on these local ECGs, these abnormalities are to be reported and thus summarized as AEs.

2.6.2.7 Vital signs

Notable vital sign values during on-treatment period will be summarized using the following criteria:

Table 2-4 Notable vital sign values

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Systolic blood pressure (mmHg)	>= 180 with increase from baseline of >= 20	<= 90 with decrease from baseline of >= 20
Diastolic blood pressure (mmHg)	>= 105 with increase from baseline of >= 15	<= 50 with decrease from baseline of >= 15
Pulse rate (bpm)	>= 100 with increase from baseline of > 25%	<= 50 with decrease from baseline of > 25%
Weight (kg)	Increase >= 10% from baseline	Decrease >= 10% from baseline
Body temperature (°C)	>= 39.1	-

2.6.3 Pharmacokinetic

2.6.3.1 Sabatolimab and venetoclax drug concentrations

Pharmacokinetic analyses will be summarized for the sabatolimab or venetoclax pharmacokinetic analysis set. 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 the dose level of sabatolimab, visit/sampling time point. Concentrations at EOT, 30-day safety follow-up and 150-day safety follow-up visit will not be included in the summary table for sabatolimab. In the case of predose samples, the actual dose would reflect the prior dose the participant received. The summary table for venetoclax concentration data only includes the patients whose prior dose (D7 dose) was 400 mg at each 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%. Sabatolimab and venetoclax concentration data obtained from samples collected outside of PK sample collection window as defined per protocol will be flagged and excluded for the summary statistics. PK parameters (the minimum observed plasma or serum drug concentration (Cmin or Ctrough) and the maximum (peak) observed plasma or serum drug concentration (Cmax)) 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 vs. time profiles with median will be displayed graphically, excluding concentrations at EOT, 30-day safety follow-up and 150-day safety follow-up visit. All concentration data for venetoclax by timepoints will be displayed graphically. The concentrations collected before dose administration on Day 8 of Cycle 3 and beyond are Ctrough for sabatolimab. If the sabatolimab pre-dose sample is collected more than +/- 3 days from the 28 day dose cycle, this concentration would be removed from the graph and summary. If the venetoclax pre-dose sample is collected more than +/- 3 hours from the 24 hours daily dose interval after the prior dose on Day 7, this concentration would be removed from the graph and summary. End of infusion concentration will be reported as Cmax.

2.6.3.2 As the half-life of venetoclax is approximately 26 hours, the sample collected at Cycle 1 Day 8 will be considered as the venetoclax trough concentration at steady state before any dose administration of 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.

The population pharmacokinetic analyses will not be conducted for the abbreviated final CSR. If there are 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.

2.6.4 Immunogenicity

2.6.4.1 Sample ADA Status

Each IG sample is assessed in a three-tiered anti-drug anti-body (ADA) testing approach. All IG samples are analyzed in the initial screening assay (first tier). Samples testing negative in the screening assay are not subject to a confirmatory assay. Samples testing positive in the screening assay are then subjected to the confirmatory assay to demonstrate that ADA are specific for the therapeutic protein product (second tier). The titer of confirmatory positive samples will be subsequently determined in the titration assay (third tier). Samples identified as positive in the confirmatory assay are considered ADA positive. Samples can test negative in either the screening or confirmatory assay but for analysis purposes they are not differentiated. The following properties of each sample will be provided in the source data:

- Result of the assay according to a pre-specified confirmatory cut point: ADA positive (yes) or ADA negative (no)
- Titer (for positive samples): numerical representation of the magnitude of ADA response.
- When titer values are below the titer cut point with minimal required dilution (MRD) and the result is reported as ‘Titer value 50 (MRD)’, it is interpreted as a POSTIVE sample with titer equal to 50. Drug tolerance level: highest drug concentration that does not interfere with the ADA detection method

- Fold titer change (i.e. x-fold): threshold for determining treatment boosted

Determinant samples are defined as samples which are not unevaluable (where unevaluable = sample where assay is not available).

The following definitions apply only to determinant samples:

- ADA-negative sample: Determinant sample where the assay is ADA negative and MBG453 PK concentration at the time of IG sample collection is less than the drug tolerance level.
- ADA-positive sample: Determinant sample where the assay is ADA positive.
- ADA-inconclusive sample: Sample where assay is the ADA is negative and MBG453 PK concentration at the time of the IG sample collection is greater than or equal to the drug tolerance level or missing

The following definitions apply only to post-baseline ADA-positive samples with a corresponding determinant baseline sample. To be classified as treatment-boosted or treatment-unaffected, both the post-baseline and baseline titer must be non-missing:

- treatment-induced ADA-positive sample: ADA-positive sample post-baseline with ADA-negative sample at baseline.
- treatment-boosted ADA-positive sample: ADA-positive sample post-baseline with a titer that is at least the fold titer change greater than the ADA-positive baseline titer.
- treatment-unaffected ADA-positive sample: ADA-positive sample post-baseline with a titer that is less than the fold titer change greater than the ADA-positive baseline titer.

NOTE: PK concentrations which are flagged for exclusion will still be used to determine ADA-inconclusive and ADA-negative samples.

Listings will be provided of sample ADA status (including titer for positive samples).

2.6.4.2 Participant ADA status

Any IG sample collected after 150 days of the last dose of sabatolimab will not be used for summaries or derivations and will only be included in the listing.

Participant ADA status is defined as follows:

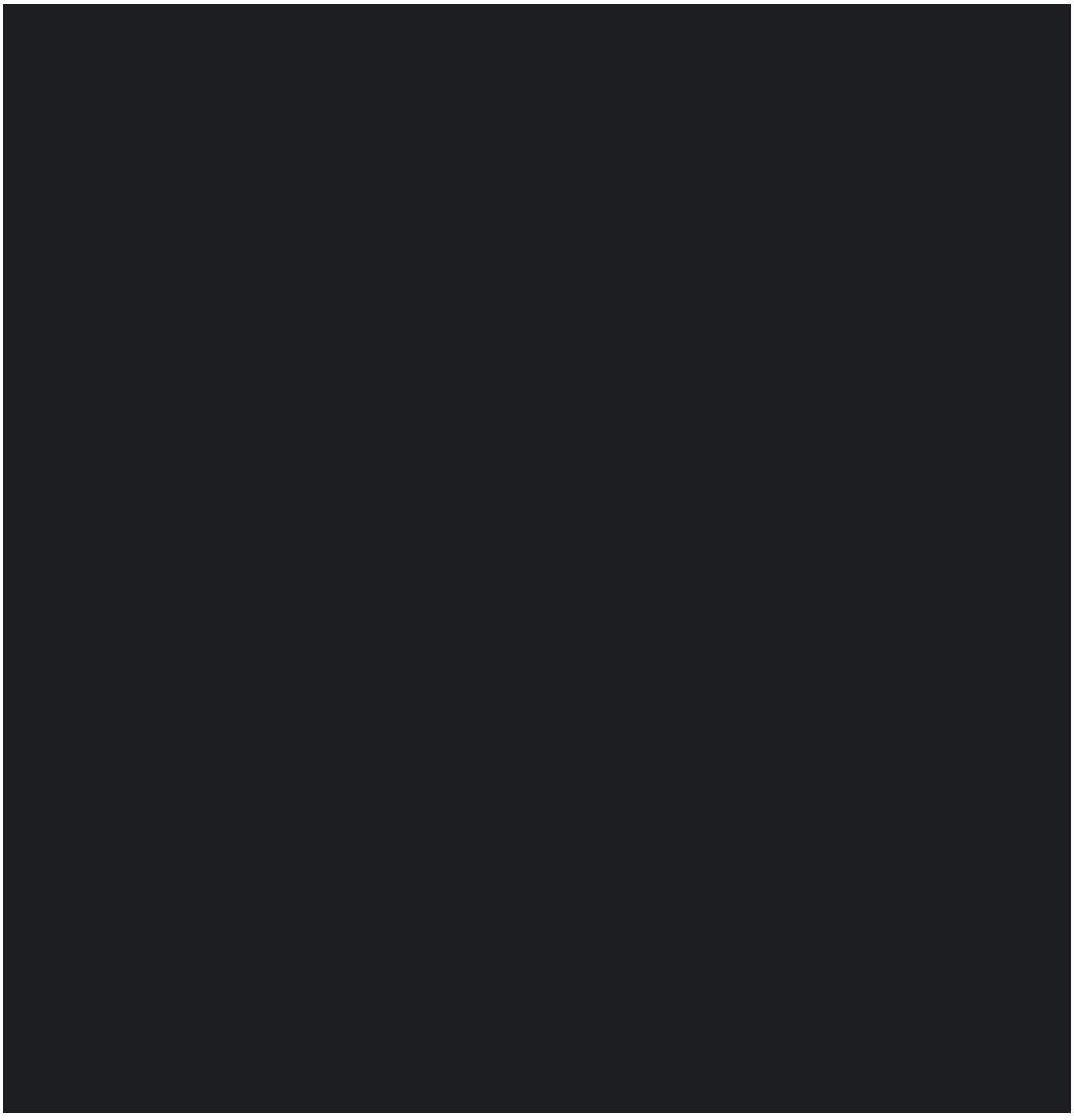
- Treatment-induced ADA-positive participant: participant with ADA-negative sample at baseline and at least one treatment-induced ADA-positive sample.
- Treatment-boosted ADA-positive participant: participant with ADA-positive sample at baseline and at least one treatment-boosted ADA-positive sample.
- Treatment-unaffected ADA-positive participant: participant with ADA-positive sample at baseline, no treatment-boosted ADA-positive samples, and at least one treatment-unaffected ADA-positive sample.
- Treatment-reduced ADA-positive participant: participant with ADA-positive sample at baseline and at least one post baseline determinant sample, all of which are ADA-negative samples.

- ADA-negative participant: participant with ADA-negative sample at baseline and at least one post baseline determinant sample, all of which are ADA-negative samples.
- Inconclusive participant: participant who does not qualify as treatment-induced ADA-positive, treatment-boosted ADA-positive, treatment-unaffected ADA-positive, treatment-reduced ADA-positive, or ADA-negative.

Listings will be provided of participant ADA status.

2.6.5 Patient-Reported outcome: MDS symptoms and fatigue (Part II only)

Not applicable.



[redacted]

2.8 Interim analysis

No formal interim analysis is planned for this trial. However, two safety review meetings during the safety run-in part and a periodic safety review by the Steering Committee will occur approximately every 6 months in the expansion cohort.

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.

For each cohort (sabatolimab 400 mg and 800 mg Q4W) of the safety run-in part, the following information (summaries and/or listings) will be provided:

- Number (%) of participants treated and included in the analysis sets
- Basic demographic and background data
- Disease characteristics and medical history
- Concomitant medications
- Patient disposition
- Protocol deviations
- Duration of exposure to study treatment, Dose intensity and relative dose intensity, Number (%) of participants with any dose changes (incl. reductions, interruptions, or permanent discontinuations) and the reasons
- DLTs, AEs, treatment related AEs, SAEs, on-treatment deaths reported during the DLT evaluation period, as well as DLTs, AEs, treatment related AEs, SAEs, on-treatment deaths reported up to the data cut-off date
- Posterior distribution for the risk of DLT for new participants at the dose level tested (see Section 2.5.2.1)
- Laboratory data and vital signs abnormalities
- Blast counts from bone marrow and investigator's response assessment

Due to the recruitment halt, safety review meetings after the safety run-in part will not be conducted.

2.9 Sample size calculation

2.9.1 Safety run-in (Part 1)

No formal statistical power calculations to determine sample size were performed for this part of the study. However, the operating characteristics are reasonable based on the sample size 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).

2.9.2 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).

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 the 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). Thus, the total sample size is comprised of 76 participants (including the 6 participants treated at 400 mg Q4W in 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 participants 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 2-5), 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 2-5 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 2-6 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.

3 Change to protocol specified analyses

As Novartis decided to halt the enrollment in the expansion part in September 2022, the following analyses as per protocol will not be performed due to data limitations:

- The primary analysis of CR rate
- The analysis of Patient-Reported outcome: MDS symptoms and fatigue
- [redacted]

4 Appendix - General definitions

Date of first administration of study treatment (sabatolimab or azacitidine or venetoclax)

The date of first administration of any study treatment component (sabatolimab or azacitidine or venetoclax) is defined as the first date when a non-zero dose of the respective study drug is administered and recorded on the study treatment eCRF page.

Date of last administration of study treatment (sabatolimab or azacitidine or venetoclax)

The date of last administration of any study treatment component (sabatolimab or azacitidine or venetoclax) is defined as the last date when a non-zero dose of the respective study drug is administered and recorded on the study treatment eCRF page. So both, first and last date of study drug, are derived separately for each drug which is part of the study treatment.

Date of first administration of study treatment (combination)

The date of first administration of study treatment (or start date of study treatment) is defined as the first date when a non-zero dose of any component of the study treatment (sabatolimab, Azacitidine or venetoclax) is administered.

Date of last administration of study treatment (combination)

The date of last administration of study treatment (or start date of study treatment) is defined as the last date when the last non-zero dose of any last component of the study treatment (sabatolimab, Azacitidine or venetoclax) is administered.

Date of last exposure to study treatment component (sabatolimab or azacitidine or venetoclax)

One planned cycle length is 28 days and the start date of a cycle is defined as the first administration of azacitidine within a cycle. Azacitidine is planned to be administered daily every cycle during 7 days at the beginning of each cycle (between Day 1 to Day 9). Sabatolimab is administered every 4 weeks (Q4W), on Day 8 of each cycle, unless there was a toxicity leading to a dosing interval increase. Venetoclax is planned to be administered once a day from day 1 to day 14 of the 28-day cycle.

The date of last exposure to sabatolimab is therefore calculated as:

- Minimum (last date of administration of sabatolimab + 27 days, date of death, last contact date in case participant is lost to follow-up), as sabatolimab injections are given Q4W.

The date of last exposure to azacitidine is calculated as:

- Minimum (last date of administration of azacitidine + 20 days, date of death, last contact date in case participant is lost to follow-up) as the 7 doses of azacitidine are given in the beginning of each cycle.

The date of last exposure to venetoclax is calculated as:

- Minimum (last date of administration of venetoclax + 14 days, date of death, last contact date in case participant is lost to follow-up) as the 14 doses of venetoclax are given in the beginning of each cycle (in case of regimen change to "one week on, three weeks off" in the last cycle, last date of administration of venetoclax + 21 days will be considered.)

End date of the last cycle initiated

The end date of the last cycle initiated is the maximum date between:

- The planned end date (Day 28) of the last cycle initiated when the last non-zero dose of any last component of the study treatment (sabatolimab or azacitidine or venetoclax) is administered,
- The actual date of the last administration of a non-zero dose of any last component of the study treatment.

The end date of the last cycle initiated (Day 28 or beyond) will be applicable even if this date goes beyond the data cut-off date (i.e., it should not be truncated to the date of data cut-off).

Date of last exposure and duration of exposure to study treatment (combination)

For the calculation of the duration of exposure to study treatment (combination), the date of last exposure to study treatment (combination) will be derived as the minimum date between:

- The latest one of the date of last exposure to any study treatment component (sabatolimab or azacitidine or venetoclax),
- Date of death,
- Last contact date in case participant is lost to follow-up.

The duration of exposure to study treatment (combination) will be calculated as follow: date of last exposure to study treatment (combination) - date of first administration of study treatment (combination) + 1.

Duration from first to last cycle initiated to calculate dose intensity and the relative dose intensity

For the calculation of the dose intensity and relative dose intensity, the duration in days from first to last cycle initiated will be calculated as follow: end date of the last cycle initiated - date of first administration of study treatment (combination) + 1.

Thus, this derivation will be irrespective of date of death or last contact date (i.e., it should not be truncated to the date of death or date of last contact date).

Study day

The study day, describes the day of the event or assessment date, relative to the reference start date (start date of study treatment).

The study day is calculated as follows:

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if event precedes the reference start date.

The reference start date for safety assessments (e.g. adverse event onset, laboratory or ECG assessment, vital sign measurement etc.) is the start of study treatment. The same reference start date will be used for efficacy (e.g. response assessment, time-to-event endpoints) and patient-reported outcomes (PRO).

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

Baseline

For efficacy evaluations and PROs, the last non-missing assessment, including unscheduled assessments on or before the date of start of study treatment is taken as "baseline" value or "baseline" assessment.

For safety evaluations, the last available assessment including unscheduled assessments on or before the date of the start of study treatment is taken as "baseline" assessment. If participants have no value as defined above, the baseline result will be missing.

Windows for multiple assessments

Time windows will be defined for descriptive summary of ECOG and PRO data (EORTC QLQC30, [redacted] by visit and the longitudinal data analysis. If more than one assessment is available in the same time window, the assessment closest to the planned date will be considered. If two assessments are obtained with the same time difference compared to the scheduled visit day, the assessment obtained prior to the visit will be considered. Data obtained at the end of treatment visit will be classified as other assessment in the corresponding time window. For participants who discontinue treatment for reasons other than progressive disease, withdraw consent or death, EORTC QLQ-C30 [redacted]5L will continue being collected every 6 months during this follow-up period until disease progression.

Table 4-1 Time windows for PRO and ECOG data

Assessment	Target day of assessment	Time Window Definition
Baseline	On or before Study Day 1[a]	≤ Study Day 1
During treatment phase		
Cycle 2 Day 1	Study Day 29	Study Days 2 to 42
Cycle 3 Day 1	Study Day 57	Study Days 43 to 70
Cycle k day 1	Study Day = 28*(k-1) + 1	Study Day

Assessment	Target day of assessment	Time Window Definition
(with k=4, 5, 6, 7, 8 etc...)		28*(k-1) +1 -14 to 28*(k-1) +14 For last cycle of dosing: from 28*(k-1) +1 -14 to end of treatment visit date +7 "Note: EOT data will be included if obtained within 7 days of permanent discontinuation of study treatment"
After treatment discontinuation (only EORTC QLQ-C30 [redacted])		
Post treatment follow-up	Every 6 months	For the first time window: [upper bound of the last previous time windows with assessment + 1; PRO assessment date + 84 days] Otherwise: [PRO assessment date -/+ 84 days]
[a] Study Day 1 = randomization date will be baseline (except for [redacted] for which there is no baseline)		

Last contact date

The last contact date will be used for censoring of participants in the analysis of overall survival.

The last contact date is defined as the latest complete date from the below list on or before the data cut-off date:

Table 4-2 Last contact date data sources

Source data	Conditions
Date of start of treatment	Non-missing dose
Last date participant was known to be alive from Survival Follow-up page	Participant status is reported to be alive or unknown
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term
Start/End dates from drug administration record	Non-missing dose
Response assessment date	Response marked as 'done'
Laboratory/PK collection dates	Sample collection marked as 'done'
Vital signs date	At least one non-missing parameter value
ECOG performance status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

The cut-off date will not be used for last contact date, unless the participant was seen or contacted on that date. No date post cut-off date will be used.

Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose record) will not be used to derive the last contact date. Partial date imputation is allowed for event (death)/censoring only if coming from the 'Survival' eCRF.

The last contact date will be derived for participants not known to have died at the analysis cut-off using the last complete date among the following:

5 Reference

- Babb J, Rogatko A, Zacks S (1998) Cancer phase I clinical trials: efficient dose escalation with overdose control. Stat Med p. 1103-20.
- Cheson BD, Bennett JM, Kopecky KJ, et al (2003) Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J. Clin. Oncol. p. 4642-9.
- Clopper CJ and Pearson ES (1934) The use of confidence or fiducial limites illustrated in the case of the binomial. p. 404-413.
- Platzbecker U (2019) Treatment of MDS. Blood p. 1096-1107.
- Platzbecker U, Fenaux P, Adès L, et al (2018) Proposals for revised IWG 2018 hematological response criteria in patients with MDS included in clinical trials. Blood; [Epub ahead of print].
- Pollyea D. et al. Venetoclax in combination with hypomethylating agents induces rapid, deep, and durable responses in patients with AML ineligible for intensive therapy. 2018 Dec 2; Oral Abstract #285: 60 ASH Annual Meeting and Exposition, San Diego, CA.
- Cheson BD, Greenberg PL, Bennett JM, et al (2006) Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood p. 419-25.\
- [redacted]
- Fayers PM (2001) Interpreting quality of life data: population-based reference data for the EORTC QLQ-C30. Eur J Cancer; 37(11): 1331-4.