NOVARTIS

Clinical Development

MBG453 (sabatolimab)

CMBG453F12201 /NCT04623216

A phase Ib/II, open label study of sabatolimab as a treatment for patients with acute myeloid leukemia and presence of measurable residual disease after allogeneic stem cell transplantation

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
10-June-2021	FPFV	Creation of version 1.0	N/A - First version (based on protocol from 30-Sep-2020)	N/A
03-Jul-2024	Before primay CSR DBL	Creation of version 2.0	Amendment 2 (based on protocol from 24-March-2022) and MBG453 program termination	Sections updated based on the protocol amendment 2 dated from 24 March 2022: • Section 1.2.1: primary safety and efficacy estimand definitions • Section 2.1: clarification of general definition Sections updated due to MBG453 program termination and thus, simplification of the analyses: • Section 1: general statement added. Addition of a column in the objectives tables to summarize the analyses performed for this final analysis. • Section 2.1: general statement added. • Section 2.3.1: simplification of protocol deviations summaries and deletion of pre-screened and screened failures analyses • Section 2.4.1: cycle delays analysis deleted • Section 2.4.2: Clarifications. Donor Lymphocyte Infusions will be only listed. • Section 2.5 and 2.6: general statement added. Following endpoints were flagged as not assessable: • Primary safety analysis in adolescents • p-value deleted for the primary efficacy analysis in adults • GvHD-free/relapse-free survival [redacted] • Section 2.7: AEs, SAEs, COVID-19 related events, GvHD, severe immune-related adverse events not attributed to GvHD, AESI and vital signs analyses simplified. Figures and corresponding tables for hematology parameters deleted • Section 2.8: PK analyses simplified [redacted] Section 2.6: Listings of all responses assessments [redacted] added.

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				Section 5: updated date of last exposure to study treatment and duration of exposure to study treatment derivation Typos corrected Clerical updates Updating of list of Abbreviatons

List of abbreviations

[redacted]	[redacted]
AE	Adverse event
AESI	Adverse events of special interest
aGvHD	Acute Graft-versus-Host disease
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic classification
BLQ	Below the limit of quantitation
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
cGvHD	Chronic Graft-versus-Host disease
CI	Confidence interval
CR	Complete remission
CRi	Complete remission with incomplete hematologic recovery
CSR	Clinical study report
CTC	Common toxicity criteria
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
DDS	Dose-determining set
DLI	Donor lymphocyte infusion
DLT	Dose limiting toxicity
DMS	Document Management System
eCRF	Electronic case report form
eCRS	Electronic case retrieval strategy
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event free survival
ELN	European Leukemia Net
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer - Quality of Life Questionnaire
EOT	End of treatment
EQ-5D-5L	EuroQol Group - standardized measure of health status questionnaire
FAS	Full analysis set
GRFS	GvHD-free/relapse-free survival
GvHD	Graft versus host disease
HSCT	Hematopoietic stem cell transplantation
[redacted]	[redacted]
IST	Immunosuppressive treatment
LAIP	Leukemia associated immunophenotype
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	Morphologic leukemia free state
MRD	Measurable residual disease

OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PGI	Patient global impression
PK	Pharmacokinetics
PR	Partial remission
PT	Preferred term
QoL	Quality of life
Q4W	Every 4 weeks
RAP	Report and analysis process
RBC	Red blood cells
RDE	Recommended dose for expansion
RFS	Relapse free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SMQ	Standardized MedDRA Query
SOC	System organ class
SoC	Standard of Care
TFLs	Tables, figures, listings
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes the planned analyses for the final Clinical Study Report (CSR) of the sabatolimab Study CMBG453F12201, A phase Ib/II, open label study of sabatolimab as a treatment for patients with acute myeloid leukemia and presence of measurable residual disease after allogeneic stem cell transplantation (aHSCT).

As specified in Section 12.7 of the study protocol, interim analyses are planned for the monitoring of safety data, and will be conducted after each dose level cohort of the safety run-in part to determine the recommended dose for expansion (RDE) (primary safety objective). This SAP will serve as the basis for those analyses as well; however, a separate selection of tables, figures and listings (TFL) will be done.

The content of this SAP is based on the CMBG453F12201 protocol amendment 2 (24-Mar-2022). All decisions regarding the analysis, as defined in the SAP document, have been made prior to database lock.

Due to the study recruitment halt and the termination of the MBG453 program for non-safety-related reasons, this study will be terminated early. Thus, not all protocol planned derivations and analyses will be performed. Although described in this document, please refer to table of endpoints for the selected planned analyses of this final CSR. Any secondary endpoint analyses not conducted due to limited number of patients available, will be documented as such in the final CSR and indicated as zero patients with an explanation for mandatory results posting, if required.

1.1 Study design

CMBG453F12201 is a phase Ib/II, open label study of sabatolimab as monotherapy and in combination with azacitidine, in participants with AML/secondary AML who have received one aHSCT and who are in complete remission (CR) as described in the study protocol Table 8-3 but measurable residual disease positive (MRD+).

The study consists of 2 parts. Part 1 is a Safety Run-in including two cohorts tested sequentially to assess whether sabatolimab as a single agent is safe in this post-aHSCT setting:

- Cohort 1: adults treated with sabatolimab as a single agent at 400 mg Q4W dose level (n~8),
- Cohort 2: adults treated with sabatolimab as a single agent at 800 mg Q4W dose level) (n~12).

Part 2 is the expansion phase to assess the efficacy, safety, pharmacokinetics (PK) and MRD status of sabatolimab in 3 different cohorts:

- Cohort 3 (combination cohort): adults treated with sabatolimab at the RDE in combination with azacitidine (n~20),
- Cohort 4 (monotherapy expansion cohort): adults treated with sabatolimab at the RDE (n~13 if the RDE is 800 mg Q4W and ~12 participants were already included in the safety run-in part at this dose level; n~17 if the RDE is 400 mg Q4W and ~8 participants were already included in the safety run-in part at this dose level),

- Cohort 5 (adolescent cohort): adolescents treated with sabatolimab as a single agent at the RDE (n ~6).

During the expansion part, adults are randomized to be enrolled either in the combination cohort (Cohort 3) or in the monotherapy expansion cohort (Cohort 4) to minimize selection bias.

A total of approximately 59 participants were planned to be enrolled in this study including approximately 25 adults treated with sabatolimab at the RDE as a single agent (Cohort 2 + Cohort 4 or Cohort 1 + Cohort 4) and approximately 20 adults treated with sabatolimab at the RDE in combination with azacitidine. The number of participants included in each study part/cohort was presented in Figure 3-1 of the protocol.

Study treatment consists of cycles of sabatolimab (400 mg or 800 mg) administered intravenous on Day 1 of each 28-day cycle for the monotherapy cohorts (Cohorts 1, 2, 4 and 5). Study treatment consists of cycles of sabatolimab (400 mg or 800 mg) administered on Day 5 of each 28-day cycle in combination with azacitidine administered intravenous or subcutaneous at 50 mg/m^2 daily during the first 5 days of each cycle (Cohort 3). Crossover between the different sabatolimab doses (400 mg and 800 mg Q4W) is not permitted at any time during the study. Study treatment may continue for up to a maximum of 24 cycles or until the participant experiences a documented hematologic relapse from CR/CRi (as defined by ELN 2017 Döhner et al 2017) or unacceptable toxicity, whichever is earlier.

Interim analyses are planned for the monitoring of safety data, and will be conducted after each dose level cohort of the safety run-in part to determine the RDE. The first safety review meeting to assess whether sabatolimab 400 mg Q4W is not meeting overdose criteria (i.e. an excessive incidence of Dose Limiting Toxicities (DLT)) will take place after at least 6 evaluable participants treated with sabatolimab 400 mg Q4W have completed 2 cycles of treatment (Cohort 1). If no safety concerned are observed at this dose level, a second safety review meeting to assess whether sabatolimab 800 mg Q4W is not meeting overdose criteria will take place after at least 9 evaluable participants treated with sabatolimab 800 mg Q4W have completed 2 cycles of treatment (Cohort 2). Details on the definition of dose limiting toxicities (DLT) are presented in study protocol Table 6-2.

The efficacy of sabatolimab when given as a single agent or in combination with azacitidine will be assessed after all adults from Cohorts 3 and 4 have completed 6 cycles of treatment (primary efficacy objective). The end of study is defined as all participants having completed the safety and post-treatment follow up (if applicable), or having died, been lost to follow-up or having withdrawn consent to further participation in the study.

Due to the study recruitment halt and the termination of the sabatolimab program for non-safety-related reasons, the study will be terminated early. Based on the limited numbers of participants, the final CSR will be written with a limited number of analyses.

1.2 Study objectives, endpoints and estimands

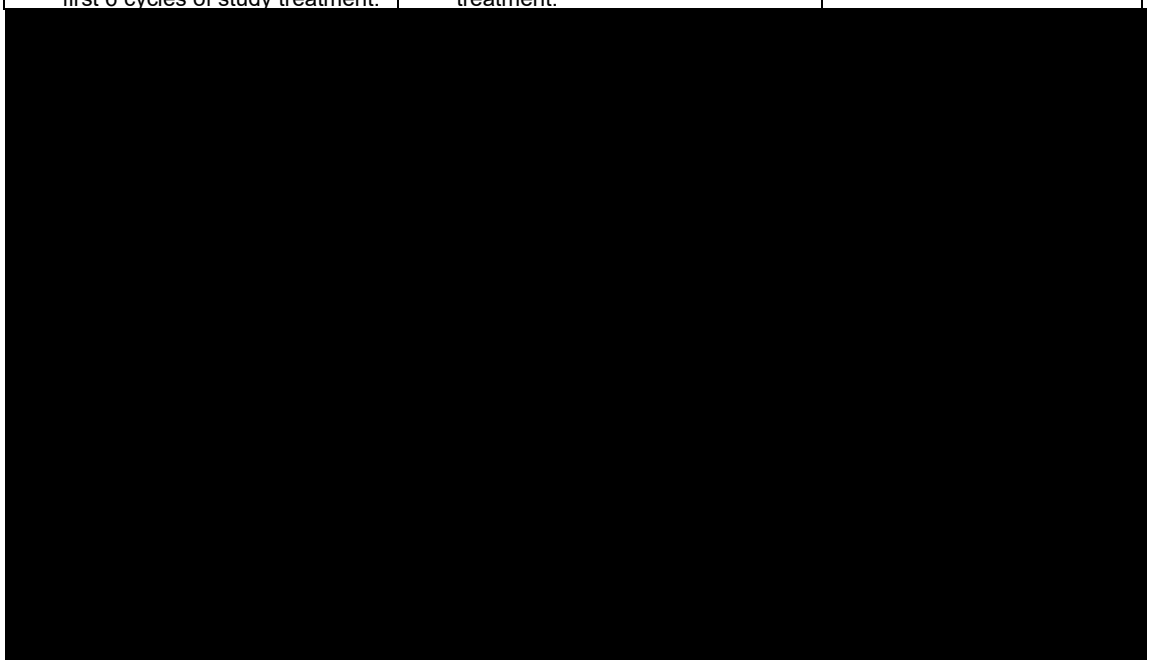
Table 1-1 (which is a copy of the Table 2-1 from the study protocol) outlines the primary, secondary [redacted] objectives and belonging endpoints. Further details are given in the statistical methods section of this SAP. Due to the study recruitment halt and the termination of the sabatolimab program for non-safety-related reasons, not all protocol planned derivations

and analyses will be performed. Although described in this document, please refer to table of endpoints for the selected planned analyses of this final CSR. Any secondary endpoint analyses not conducted due to limited number of patients available, will be documented as such in the final CSR and indicated as zero patients with an explanation for mandatory results posting, if required. [redacted]

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)	Final CSR
Primary objective(s)	**Endpoint(s) for primary objective(s)**	**Endpoint(s) selected**
• For adults only (from the safety run-in part): To determine whether sabatolimab as monotherapy at the two tested dose levels (400 mg and 800 mg Q4W) leads to an unacceptable level of toxicity when administered to adult participants with AML who are in complete remission but are MRD+ post-aHSCT.	• Incidence of treatment-emergent dose limiting toxicities (DLTs), including aGvHD and cGvHD during the first 2 cycles of study treatment.	• Yes
• For adults only (from both safety run-in and expansion parts): To evaluate preliminary efficacy of sabatolimab (at the recommended dose level for expansion) as monotherapy and in combination with azacitidine on prevention of hematologic relapse by assessing the proportion of adult participants with AML and MRD+ post-aHSCT (according to local assessment) who remain with no evidence of hematologic relapse after 6 cycles of study treatment.	• The proportion of adult participants for whom no evidence of hematologic relapse (no evidence of bone marrow blasts ≥5%; no evidence of reappearance of blasts in the blood; no evidence of development of extramedullary disease) have been documented after 6 cycles of study treatment (per investigator assessment).	• Yes
• For adolescents only: To determine whether sabatolimab as monotherapy at the recommended dose level for adults leads to an unacceptable level of toxicity when administered to adolescent participants with AML who are in complete remission but are MRD+ post-aHSCT.	• Incidence of treatment-emergent dose limiting toxicities (DLTs), including aGvHD and cGvHD during the first 2 cycles of study treatment.	• No
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**	
• To assess the incidence of grade III or IV aGvHD and moderate to severe cGvHD.	• Incidence of treatment emergent grade III or grade IV aGvHD. • Incidence of treatment emergent moderate to severe cGvHD.	• No

Objective(s)	Endpoint(s)	Final CSR
• To characterize the pharmacokinetics (PK) of sabatolimab.	• Summary of serum concentrations (pre-dose samples) and pharmacokinetic parameters (the minimum observed plasma or serum drug concentration: Cmin) for sabatolimab.	• Yes
• To assess GvHD-free/relapse-free survival (GRFS).	• Time from start of treatment to the date of first documented occurrence or worsening of treatment emergent grade III or IV aGvHD or moderate to severe cGvHD requiring initiation of systemic treatment, hematologic relapse, or death due to any cause, whichever occurs first.	• No
• To assess Relapse-Free Survival (RFS).	• Time from start of treatment to the date of first documented hematologic relapse or death due to any cause, whichever occurs first.	• Yes
• To determine the safety and tolerability of sabatolimab in monotherapy and in combination with azacitidine.	• Incidence and severity of AEs and SAEs, changes in laboratory values and vital signs.	• Yes
• To assess severe immune-related adverse events not attributed to GvHD.	• Incidence of treatment-emergent ≥ grade 3 immune-related adverse events not attributed to GvHD.	• Yes
• To assess the proportion of participants with centrally confirmed MRD+ at screening who become MRD- during the first 6 cycles of study treatment.	• Proportion of participants with centrally confirmed MRD+ status at baseline converting to MRD- within the first 6 cycles of study treatment.	• Yes



Objective(s)	Endpoint(s)	Final CSR
[redacted]		

1.2.1 Primary estimands

For adults participants included in this study, there are two primary clinical questions:

- Safety: Does sabatolimab, administered as monotherapy at 400 mg and 800 mg Q4W dose levels, lead to an unacceptable level of toxicity [dose-limiting toxicity (DLT)], when given to treat participants with acute myeloid leukemia (AML) who have received an allogeneic hematopoietic stem cell transplantation (aHSCT), and are in complete remission but are MRD+ (per local assessment)?
- Efficacy: What is the effect of sabatolimab at the RDE, as monotherapy and in combination with azacitidine, on prevention of hematologic relapse (i.e., no evidence of bone marrow blasts ≥ 5%, no evidence of reappearance of blasts in the blood, no evidence of development of extramedullary disease) [i.e., maintenance of complete remission (CR) or CR with incomplete hematologic recovery (CRi)] in participants with AML at high risk of relapse (MRD positivity as per local assessment) after aHSCT regardless of treatment interruption or discontinuation during study and until use of donor lymphocyte transfusions (DLIs) or other new antineoplastic therapies?

For adolescent participants included in this study, there is one primary clinical question:

- Safety: Does sabatolimab administered as monotherapy at the recommended dose level for adults, lead to an unacceptable level of toxicity (DLT), when given to treat adolescents with AML who have received an aHSCT, have been tapered off of systemic immunosuppressive therapy at enrollment, and are in complete remission but are MRD+ (per local assessment)?

Justification: In this proof-of-concept study, the primary purpose is to determine whether or not the risk of developing GvHD, immune-related toxicities and other unacceptable toxicities is not exacerbated when sabatolimab is administered in the post-transplant setting. The activity of sabatolimab is assessed based on the absence of hematologic relapse (no evidence of any of the following: bone marrow blasts ≥5%; reappearance of blasts in the blood; or development of

extramedullary disease), which is the most clinically meaningful endpoint in this post-transplant setting where complete hematologic recovery may be delayed early post-transplant.

The **primary safety estimand for adult participants** included in this study is described by the following attributes:

1. Population: Adult participants with AML who are in CR after aHSCT and are at high risk of relapse defined as positive MRD (by local assessment) any time at Day ≥ Day 60 after aHSCT (with a confirmed MRD positivity at least 2 weeks after systemic immunosuppression has been tapered off) and who are exposed to study treatment for at least 2 cycles (minimum exposure criterion defined in the protocol Section 12.1) or who experienced a DLT within the DLT observation period.
2. Primary variable: Proportion of adult participants who experience at least one DLT including but not limited to aGvHD and cGvHD as per investigator assessment between Cycle 1 Day 1 (first administration of sabatolimab) and end of Cycle 2 (Day 28).
3. Treatment of interest: Treatment with sabatolimab as monotherapy at 400 mg and 800 mg Q4W dose levels taken for the entire study duration post aHSCT.
4. Handling of remaining intercurrent events:
    - Delay to start Cycle 3 due to any reason: a DLT that will occur after Day 28 of Cycle 2 and before starting Cycle 3 will be considered in the analysis (treatment policy strategy).
    - Failure to start Cycle 3 due to any reason: a DLT that will occur up to the theoretical last day of Cycle 2 (Cycle 2 Day 28) will be considered in the analysis regardless of permanent discontinuation after the dose of sabatolimab in Cycle 2 (treatment policy strategy).
5. Summary measure for the primary safety estimand is the proportion of participants with treatment-emergent dose limiting toxicity as per investigator assessment reported during the first 2 cycles.

The **primary efficacy estimand** for adult participants included in this study are described by the following attributes:

1. Population: Adult participants with AML who are in CR after aHSCT and are at high risk of relapse defined as positive MRD at baseline any time at ≥ Day 60 after aHSCT (with a confirmed MRD positivity at least 2 weeks after systemic immunosuppression has been tapered off).
2. Primary variable: Proportion of adult participants who remain with no evidence of hematologic relapse (no evidence of any of the following: bone marrow blasts ≥5%; reappearance of leukemic blasts in the blood; or development of extramedullary disease) as per investigator assessment 6 cycles after starting study treatment.
3. Treatment of interest: Treatment with sabatolimab or sabatolimab in combination with azacitidine taken for the entire study duration post aHSCT. One estimand for each of the two treatments of interest (sabatolimab in monotherapy and sabatolimab in combination with azacitidine) will be considered.
4. Handling of intercurrent events:

- Failure to complete 6 cycles of treatment due to death for any reason or relapse: a participant who dies or has a relapse before completing 6 cycles of treatment will be considered as a non-responder (composite variable strategy).
- Start of donor lymphocyte infusions (DLI) or a new anti-neoplastic therapy before completing 6 cycles of study treatment: a participant who starts a DLI or a new antineoplastic therapy before completing 6 cycles of treatment will be considered as a non-responder (composite variable strategy).
- Failure to complete 6 cycles of treatment due to reasons other than relapse and death for any reason (including due to adverse events, graft vs. host disease for example): all participants with an adequate response assessment (other than "unknown" response) will be taken into account regardless of any study treatment interruption or permanent discontinuation; for a participant who stops the study due to reasons other than relapse or death, we will ask the participant to perform a response assessment 6 months after starting study treatment; a participant with no evidence of hematologic relapse 6 months after starting treatment will be considered a responder (treatment policy strategy).

5. Summary measure for the primary efficacy estimand is the proportion of participants with no evidence of hematologic relapse with its exact 95% confidence interval for each of the two study treatment of interest: sabatolimab in monotherapy and sabatolimab in combination with azacitidine. The trial will be successful if at least one of the treatments of interest (sabatolimab monotherapy or sabatolimab in combination with azacitidine) meets both statistical and clinical significance.

The **primary safety estimand for adolescent participants** included in this study is described by the following attributes:

1. Population: Adolescent participants with AML who are in CR after aHSCT and at high risk of relapse defined as positive MRD any time at ≥ Day 60 after aHSCT (with a confirmed MRD positivity at least 2 weeks after systemic immunosuppression has been tapered off) and who are exposed to study treatment for at least 2 cycles or who experienced a DLT within the DLT observation period.
2. Primary variable: Proportion of adolescent participants who experience at least one DLT including but not limited to aGvHD and cGvHD as per investigator assessment between Cycle 1 Day 1 (first administration of MBG453) and end of Cycle 2 (Day 28).
3. Treatment of interest: Treatment with sabatolimab as monotherapy at the recommended dose for adults taken for the entire study duration post aHSCT.
4. Handling of remaining intercurrent events:
    - Delay to start Cycle 3 due to any reason: a DLT that will occur after Day 28 of Cycle 2 and before starting Cycle 3 will be considered in the analysis (treatment policy strategy).
    - Failure to start Cycle 3 due to any reason: a DLT that will occur up to the theoretical last day of Cycle 2 (Cycle 2 Day 28) will be considered in the analysis regardless of permanent discontinuation after the dose of sabatolimab in Cycle 2 (treatment policy strategy).

5. Summary measure for the primary safety estimand is the proportion of participants with treatment-emergent dose limiting toxicity as per investigator assessment reported in the first 2 cycles.

As Novartis decided to permanently hold recruitment on December 20th 2023 for non-safety-related reasons, the study enrolled only one adolescent in part 2. Thus, all analyses on the adolescent cohort could not be performed and only listings will be provided. Therefore this objective could not be evaluated.

2 Statistical methods

2.1 Data analysis general information

As Novartis decided to halt enrollment of the study in December 2023 for non-safety related reasons, the study data will be analyzed and reported based on all data up to last patient last visit in an abbreviated final Clinical Study Report (CSR).The final 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.

Data included in the analysis / data cut-off handling

For each of the safety review meetings a data cut-off date will be determined after the targeted number of participants has 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, extramedullary disease assessment, MRD assessment 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 2.10.

For the primary analysis, a data cut-off date will be established after all adults have completed 6 cycles of treatment (and completed the bone marrow aspirate or biopsy at Cycle 7 Day 1) or discontinued earlier. All 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. Due to the study recruitment halt and the termination of the sabatolimab program for non-safety related reasons, the primary analysis will be the final analysis performed with the last patient last visit date, as the cut-off date.

Whatever the planned analysis, any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations regardless of when data were collected after the cut-off date.

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).

General definitions

"Investigational drug" refers to sabatolimab.

"*Study treatment"* refers to the combination of sabatolimab plus azacitidine or sabatolimab alone in the monotherapy cohorts.

"Study treatment component" or "study drug" refers to sabatolimab or azacitidine.

Other general definitions are detailed in Appendix Section 5.1.

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 overtoxicity 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 the final analysis, the analysis sets defined below will include participants from both the safety run-in and the expansion parts. Participants will be analyzed according to the study treatment and the sabatolimab dose regimen they have been assigned to, as well as by the age group (adults versus adolescent). Thus, results will be presented by considering 4 dose cohorts:

- Adults with sabatolimab 400 mg (Cohort 1 + Cohort 4 if the RDE is 400 mg Q4W)
- Adults with sabatolimab 800 mg (Cohort 2 + Cohort 4 if the RDE is 800 mg Q4W)
- Adults with azacitidine & sabatolimab combination (Cohort 3)
- Adolescents with sabatolimab monotherapy (Cohort 5)

Full Analysis Set

The Full Analysis Set (FAS) comprises all participants who received at least one dose of any component of the study treatment (i.e. at least one dose of sabatolimab or at least one dose of azacitidine).

Safety Set

The Safety Set includes all participants from the FAS.

Dose-Determining Set

The Dose-Determining Set (DDS) includes all participants from the FAS enrolled in the safety run-in part and in the adolescent cohort (Cohort 5) who met the minimum exposure criterion described in the protocol Section 12.1 and had sufficient safety evaluations, or experienced a dose limiting toxicity (DLT) between Cycle 1 Day 1 (first dose of sabatolimab) and the end of

Cycle 2 (both inclusive). Details on the definition of dose limiting toxicities (DLT) are presented in study protocol Table 6-2. A participant will be considered evaluable for DLT if:

- Participant has received 2 infusions of sabatolimab at the assigned dose level in Q4W dosing regimen, and participant has had safety assessments for a minimum period of 2 cycles (from Cycle 1 Day 1 to the end of Cycle 2), or
- Participant has experienced a DLT within the DLT observation period from first dose of sabatolimab to the end of Cycle 2.

Note: For a participant with a grade 4 neutropenia, thrombocytopenia and pancytopenia (hematological toxicity that could be qualified as a DLT) occurred during the DLT evaluation period (from Cycle 1 Day 1 to the end of Cycle 2), a sufficient follow-up time will be considered to determine if the adverse event has to be qualified as a DLT.

Note: The period from Cycle 1 Day 1 to the day before Cycle 3 Day 1 corresponds to the period from the first dose of sabatolimab in Cycle 1 to the day before the first dose of sabatolimab in Cycle 3. In case of Cycle 3 is not initiated, the period to consider for the DLT evaluation will be the period from the first dose of sabatolimab in Cycle 1 to the theoretical last day of Cycle 2 (Cycle 2 Day 28).

Pharmacokinetic Analysis Sets

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

For a concentration to be evaluable:

- Dosing information must be properly documented (data and time of administration)
- For post-dose samples: planned dose of sabatolimab must be taken prior to sampling
- For pre-dose samples: the sample is collected before the next dose administration

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	Did 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

Withdrawal of Informed Consent

Any data collected in the clinical database after a participant withdraws the informed consent from all further participation in the study will not be included in the analyses. The date on which a participant withdraws the 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 an informed consent or after withdrawal of consent will not be included in the analyses.

2.2.1 Subgroup of interest

Not applicable.

2.3 Participant disposition, demographics and other baseline characteristics

The FAS will be used for the analyses below. Participant disposition, demographics and other baseline characteristics will be summarized by dose cohort (Adults with sabatolimab 400 mg, Adults with sabatolimab 800 mg, Adults with azacitidine and sabatolimab combination, Adolescents with sabatolimab monotherapy).

2.3.1 Participant disposition

Number (%) of participants screened and enrolled will be summarized by country and center.

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

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

2.3.2 Demographic and other baseline/disease characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively for all participants from the FAS.

BMI (kg/m^2) 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 AML diagnosis (initial diagnosis, ELN classification, current disease status (de novo or secondary) and cytogenetic abnormalities will be tabulated and time since diagnosis summarized.

Details on allogeneic transplant history (disease remission status at time of transplant, transplantation timing, etc. as well as history of acute Graft-versus-Host Disease (GvHD) and chronic GvHD) will be tabulated and time since transplant summarized.

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 cohort (Adults with sabatolimab 400 mg, Adults with sabatolimab 800 mg, Adults with azacitidine & sabatolimab combination, Adolescents with sabatolimab monotherapy).

2.4.1 Study treatment / compliance

The duration of exposure to sabatolimab, azacitidine, and to the combination sabatolimab+azacitidine for the combination cohort only, as well as the actual dose intensity, relative dose intensity, dose changes, will be summarized by descriptive statistics.

Duration of exposure

The duration of exposure (in months) will be summarized for study treatment (combination) and for each study drug individually (sabatolimab and azacitidine) 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 5.1.

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 is used for BSA:

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

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 drugs is the ratio of planned cumulative dose and duration in days from first to last cycle initiated:

- For sabatolimab the planned dose intensity is 400 mg/28 days or 800 mg/28 days,
- For azacitidine, the planned dose intensity is 50 mg/m^2/day which is equivalent to 250 mg/m^2/28 days,

The relative dose intensity is then computed as the ratio of actual dose intensity and planned dose intensity. As 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 5.1.

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 drug. 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).

2.4.2 Prior, concomitant and post therapies

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be 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. Prior surgical and medical procedures will be summarized by SOC and PT.

Anti-neoplastic medications and cellular therapies after discontinuation of study treatment during follow-up within the study will be summarized by ATC class and preferred term. Donor lymphocyte infusions (DLI) will be listed.

2.5 Analysis of the primary objective

For adults, the primary safety objective is to determine whether sabatolimab given in monotherapy at the tested dose level (400 mg and 800 mg) leads to an unacceptable level of toxicity including treatment emergent aGvHD and cGvHD and to determine the dose recommended for expansion (RDE).

For adolescents, the primary objective is to determine whether sabatolimab given in monotherapy at the recommended dose for adults does not lead to an unacceptable level of toxicity in adolescents. Following Novartis decision to permanently hold recruitment for non-safety related reasons, only one adolescent was enrolled in part 2. Thus, all analyses on the adolescent cohort could not be perform and only listings will be provided.

The primary efficacy objective is to assess the proportion of adult participants with AML and MRD+ post-aHSCT (according to local assessment) who remain with no evidence of hematologic relapse after 6 cycles of study treatment for each cohort (sabatolimab at the RDE in monotherapy and sabatolimab at the RDE in combination with azacitidine).

2.5.1 Primary endpoints

Primary safety analysis in adults (safety run-in part only)

The primary endpoint is the incidence of DLTs between Cycle 1 Day 1 and the end of Cycle 2 of treatment in participants enrolled in the safety run-in part and included in the DDS.

Details on the definition of DLT which are to be captured in the Adverse Event eCRF are defined in Table 6-2 in the protocol.

Primary safety analysis in adolescent (Cohort 5 only) – Not assessable

The primary endpoint is the incidence of DLTs between Cycle 1 Day 1 and the end of Cycle 2 of treatment in participants enrolled in the adolescent cohort (Cohort 5) and included in the DDS.

The same definition of DLT is applied for adolescents and adults.

Primary efficacy analysis in adults (safety run-in and expansion parts)

The primary endpoint is the proportion of participants included in the FAS with no evidence of hematologic relapse after 6 cycles of study treatment or discontinue earlier for adults treated with sabatolimab at the recommended dose for expansion (RDE) in monotherapy and separately for adults treated with sabatolimab in combination with azacitidine.

Details on the definition of response categories which are to be captured in the eCRF by the investigator are defined in Table 8-3 of the protocol.

2.5.2 Statistical hypothesis, model, and method of analysis

Primary safety analysis in adults (safety run-in part only)

A Bayesian model will be used to assess whether sabatolimab at the two tested dose levels is not meeting an unacceptable level of toxicity in adults from the DDS. The threshold to qualify for an acceptable level of toxicity was higher (50%) than the standard threshold used in phase I study (33%) because:

- aGvHD and cGvHD are included in the DLT definition,
- Yet, the curative efficacy of aHSCT is attributable to GvL, which inherently maybe associated with risk of GvHD,
- Therefore, post-aHSCT immunomodulatory interventions, including sabatolimab, that promote GvL could potentially induce GvHD and other immune-related adverse events.

The relationship between the dose of sabatolimab and the probability of DLT is modeled using a logistic regression detailed in Appendix Section 16.6 of the protocol. A summary of the characteristics of this Bayesian model is presented below:

- A single agent dose-DLT logistic model will assess the toxicity risk of sabatolimab.
- Taking into account the lack of historical data and the intrinsic risk of GvHD (which is part of the DLT definition) in the post-aHSCT setting, a weakly informative priors with means corresponding to a risk of DLT at the reference dose of 15%, and a doubling in dose leading to a doubling in the odds of the risk of a DLT were selected.

- The prior risk of excessive toxicity (i.e. risk of DLT within [50%-100%]) is 10.3% for the sabatolimab 400 mg Q4W and 19.4% for the sabatolimab 800 mg Q4W.

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 [50%, 100%] (i.e. excessive toxicity). After the first cohort, if this posterior probability is less than 25% for the two dose levels (400 mg and 800 mg), it would be recommended to start enrolling participants in Cohort 2 with sabatolimab 800 mg Q4W dose level.

Primary safety analysis in adolescent (Cohort 5 only) - Not assessable

The same Bayesian dose-DLT model will be used for the adolescent cohort (Cohort 5) if we have at least 3 participants evaluable in the DDS. The posterior probability that the risk of DLT for adolescents treated with sabatolimab at the dose recommended for adults lies within the interval [50%, 100%] (i.e. excessive toxicity) will be presented.

Primary efficacy analysis in adults (safety run-in and expansion parts)

A Bayesian design will be used to estimate the proportion of participants with no evidence of hematologic relapse after 6 cycles of study treatment in adults from the FAS treated with sabatolimab at the RDE in monotherapy and separately for adults treated with sabatolimab in combination with azacitidine, and to provide inferential summaries (e.g. mean, standard deviation, 95% credible intervals, and interval probabilities). This dual-criterion design will allow for base trial success not only on the statistical significance for superiority against the effect size expected with the Standard of Care (SoC) (the "null-value"), but also by considering a minimum clinically estimated effect size (the "decision value").

The decision criteria for trial success for adult participants treated with sabatolimab in monotherapy (participants enrolled in Cohorts 1, 2, 4 and treated at the RDE) are the following:

1. Statistical decision rule: the posterior probability that the proportion of adult participants who remain with no evidence of hematologic relapse after 6 cycles of study treatment is $\geq$ 15% is at least 97.5% (statistical significance at 2.5% level, 1-sided).
2. Clinical decision rule: the posterior median for the proportion of adult participants who remain with no evidence of hematologic relapse after 6 cycles of study treatment is $\geq$ 30%.

The decision criteria for trial success for adults participants treated with sabatolimab in combination with azacitidine (participants enrolled in Cohort 3, "combination cohort") are the following:

3. Statistical decision rule: the posterior probability that the proportion of adult participants who remain with no evidence of hematologic relapse after 6 cycles of study treatment is $\geq$ 30% is at least 97.5% (statistical significance at 2.5% level, 1-sided).
4. Clinical decision rule: the posterior median for the proportion of adult participants who remain with no evidence of hematologic relapse after 6 cycles of study treatment is $\geq$ 50%.

Inferential summaries (e.g. mean, median, standard deviation and 95% credible intervals) based on the Bayesian posterior distribution of the proportion of participants without a documented hematologic relapse will be presented by treatment arm (sabatolimab monotherapy and

sabatolimab in combination with azacitidine). The results will also be presented with a frequentist formulation: the proportion of adult participants who remain with no evidence of hematologic relapse after 6 cycles of study treatment and the exact 95% confidence interval (Clopper and Pearson 1934), as well as the 1-sided p-value will be provided by treatment arm respectively (sabatolimab monotherapy and sabatolimab in combination with azacitidine). No adjustment of the type I error for multiplicity is planned for this study. The p-value will not be assessed due to the limited number of participants.

2.5.3 Handling of intercurrent events

Handling of intercurrent events of the primary efficacy and safety estimands is described in Section 1.2.1.

2.5.4 Handling of missing values not related to intercurrent event

Primary efficacy analysis in adults (safety run-in and expansion parts)

For a participant who completed at least 6 cycles of treatment or who discontinued treatment earlier before completion of 6 cycles (for reasons other than death, relapse or start of new anti-neoplastic therapy) and the response assessment on Cycle 7 Day 1 (after completing 6 cycles) or 6 months after start of study treatment (if 6 cycles were not completed) is missing or the response is "unknown":

- If no relapse (maintenance of CR or CRi) is documented at the subsequent response assessment (any time after Cycle 7 Day 1 or 6 months after study entry if 6 cycles are not completed), the participant will be considered a responder.
- If a relapse (no maintenance of CR or CRi) is documented in the subsequent response assessment (any time after Cycle 7 Day 1 or 6 months after study entry if 6 cycles are not completed), the participant will be considered a non-responder.
- If the subsequent response assessment (any time after Cycle 7 Day 1 or 6 months after study entry if 6 cycles are not completed) is also missing or the response is "unknown", the participant will be considered as a non- responder.

2.5.5 Sensitivity analyses

Not applicable.

2.5.6 Supportive analyses

Not applicable.

2.6 Analysis of secondary objective(s)

Secondary efficacy endpoints will be analyzed and summarized for the FAS and by dose cohort (Adults with sabatolimab 400 mg, Adults with sabatolimab 800 mg, Adults with azacitidine and sabatolimab combination, Adolescents with sabatolimab monotherapy).

A listing of all responses assessments by participant will be provided.

2.6.1 Secondary endpoints

Relapse-Free Survival (RFS)

RFS is defined as the time from start of treatment to the date of first documented hematologic relapse or death due to any cause, whichever occurs first. RFS will be censored if no RFS event is observed before the first to occur between: (i) the analysis cut-off date, (ii) the date when a new anti-neoplastic therapy or a donor lymphocyte infusion (DLI) is started, and (iii) lost to follow-up or withdrawal of consent. The censoring date will be the date of the last adequate response assessment prior to cut-off/start of new anti-neoplastic therapy or DLI. The handling of intercurrent events will be the same as the primary estimand.

RFS will be analyzed in the FAS population and the RFS distribution will be estimated using the Kaplan-Meier method. Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each dose cohort.

The following events could occur during the study and may affect the interpretation of the results:

- Start of donor lymphocyte infusions (DLI) or a new anti-neoplastic therapy: For a participant without an event before the time he/she receives any DLI or further anti-cancer therapy, RFS would be censored at the date of the last adequate assessment prior to start of DLI or further anti-neoplastic therapy.
- Stopping study treatment (including due to toxicities): All events will be taken into account when they occur, regardless of any study treatment interruption or permanent discontinuation.
- Discontinuation from study due to lost to follow-up or withdrawal of consent: For a participant without an event prior to discontinuation due to lost to follow-up or withdrawal of consent, RFS will be censored at the last adequate assessment date.

In case of two or more missing assessments prior to documented relapse or death, RFS will be censored at the last adequate response assessment prior to the documentation of relapse or death. The rule to determine whether there are two missing assessments is described in Section 2.6.3.

The RFS censoring reason will be summarized as:

1. Ongoing without event
2. New anti-neoplastic therapy
3. Donor lymphocyte infusions
4. Withdrew consent
5. Lost to follow-up
6. Event documented after two or more missing response assessments

GvHD-free/relapse-free survival (GRFS) – Not assessable

GRFS is defined as the time from start of treatment to the date of first documented occurrence or worsening of treatment emergent grade III or IV aGvHD or moderate to severe cGvHD requiring initiation of systemic treatment, hematologic relapse, or death due to any cause, whichever occurs first. GRFS will be censored if no GRFS event is observed before the first to occur between: (i) the analysis cut-off date, (ii) the date when a new anti-neoplastic therapy, or a donor lymphocyte infusion (DLI) is started, and (iii) lost to follow-up or withdrawal of consent.

The censoring date will be the date of the last adequate response assessment prior to cut-off/start of new anti-neoplastic therapy or DLI.

GRFS will be analyzed in the FAS population and the GRFS distribution will be estimated using the Kaplan-Meier method. Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each dose cohort.

The following events could occur during the study and may affect the interpretation of the results:

- Start of donor lymphocyte infusions (DLI) or a new anti-neoplastic therapy: For participant without an event before the time he/she receives any DLI or further anti-cancer therapy, GRFS will be censored at the date of the last adequate assessment prior to start of DLI or further anti-neoplastic therapy.
- Stopping study treatment (including due to toxicities): All events will be taken into account when they occur, regardless of any study treatment interruption or permanent discontinuation.
- Discontinuation from the study due to lost to follow-up or withdrawal of consent: For participants without an event prior to discontinuation due to lost to follow-up or withdrawal of consent, GRFS will be censored at the last adequate assessment date.

In case of two or more missing assessments prior to documented relapse or death or treatment emergent grade III or IV aGvHD, or moderate to severe cGvHD requiring initiation of systemic treatment, GRFS will be censored at the last adequate response assessment prior to the documentation of the event. The rule to determine whether there are two missing assessments is described in Section 2.6.3.

The GRFS censoring reason will be summarized as:

1. Ongoing without event
2. New anti-neoplastic therapy
3. Donor lymphocyte infusions
4. Withdrew consent
5. Lost to follow-up
6. Event documented after two or more missing response assessments

MRD conversion rate based on central MFC-MRD assessment from BMA

MRD conversion rate is defined as the proportion of participants with centrally confirmed MRD+ status at baseline converting to MRD- as per central review within the first 6 cycles of study treatment. MRD-negativity will be defined as frequency of LAIP below 0.1%, as determined by a MFC-AML MRD assay by central review. A total of 4 post-baseline bone marrow aspirate or biopsy assessments is planned to be performed during the first 6 cycles of treatment (on Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1 and Cycle 7 Day 1). A participant with at least one post-baseline MRD-negative sample as per central review will be considered as having reached MRD-negativity regardless of the subsequent MRD assessments and regardless of treatment interruption or discontinuation. Only MRD samples collected before start of new anti-neoplastic therapy or DLI will be considered for this analysis.

MRD conversion rate will be analyzed in the FAS population and will be provided with exact 95% confidence interval for each dose cohort.

Local MRD assessment will be listed including chimerism data used for inclusion criteria.

2.6.2 Statistical hypothesis, model, and method of analysis

No formal statistical tests will be performed for any of the secondary efficacy endpoints and hence no multiplicity adjustment will be applied.

2.6.3 Handling of missing values

For RFS analysis, the rule to determine whether there are two missing assessments 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 on Day 1 at Cycles 2, 3 and 4 (4 weeks +/- 1 week), then every 3 cycles (12 weeks +/- 2 weeks) until Cycle 13 and every 6 months (24 weeks +/- 4 weeks) thereafter. Therefore, for the cycles until Cycle 4, any distance larger than D_2 = 2*5 weeks = 10 weeks (2.5 months) between last adequate assessment and the event means that there are two missing assessments. For the period between Cycle 4 and Cycle 13, any distance larger than D_2 = 2*14 weeks = 28 weeks (7 months) means that there are two missing assessments. And finally, for the period beyond Cycle 13, any distance larger than D_2 = 2*28 weeks = 56 weeks (1 year) means that there are two missing assessments.

2.7 Safety analyses

Safety analyses will be summarized for the safety set and by dose cohort (adults with sabatolimab 400 mg, adults with sabatolimab 800 mg, adults with azacitidine & sabatolimab combination, adolescents with sabatolimab monotherapy).

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

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

1. Pre-treatment period: from day of participant's informed consent to the day before the first administration of study treatment
2. On-treatment period: from the date of the first administration of study treatment to 30 days after the date of the 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 the first administration of study treatment to 150 days after the last dose of sabatolimab.

2.7.1 Adverse events (AEs)

Summary tables for adverse events (AEs) will include all AEs that started or worsened during the on-treatment period, including acute Graft-versus-Host Disease (GvHD) and chronic GvHD. When specified, some AEs summaries will include all AEs occurring during the overall safety period.

The number (and percentage) of participants with treatment emergent adverse events will be summarized by primary system organ class (SOC), preferred term (PT) and maximum CTCAE grade. 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 PT 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 SOC will be presented alphabetically, and the PT will be sorted within primary SOC in descending frequency. The sort order for the PT will be based on their frequency in the highest dose level of sabatolimab. 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 drugs, and outcome or action taken:

- AEs (by SOC and by PT) and separately those considered related to study drugs
- SAEs
- SAEs with the number of occurrences (an occurrence is defined as > 1 day between start and prior end date of record of same PT)
- Non-SAEs
- SAEs with fatal outcome
- AEs leading to sabatolimab permanent discontinuation

In addition, all AEs and SAE by SOC and PT will be provided on the overall safety period. All reported AEs will be listed and those that started during the pre-treatment, on-treatment and post-treatment period will be flagged.

2.7.1.1 Grade III or IV aGvHD and moderate to severe cGvHD

Separate listings including information on the maximum GvHD stage by organ will be provided for:

- treatment emergent grade III or grade IV acute GvHD
- treatment emergent moderate to severe chronic GvHD

2.7.1.2 Severe immune-related adverse events not attributed to GvHD

Treatment-emergent ≥ grade 3 immune-related adverse events not attributed to GvHD will be described in the AE listing.

2.7.1.3 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 the 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; and Customized MedDRA queries, CMQ) may also be used. NMQ and CMQ are 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. Unlike a NMQ, the CMQ is more specific for a particular compound. Both 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 the on-treatment period will be summarized together with the individual preferred terms in that grouping.

2.7.2 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 deaths reasons by SOC 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.

2.7.3 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 v5.0, 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, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase. The number (%) of participants with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized.

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

2.7.4 Other safety data

Safety data listed in this section will be listed for the safety set and presented by dose cohort (Adults with sabatolimab 400 mg, Adults with sabatolimab 800 mg, Adults with azacitidine and sabatolimab combination, Adolescents with sabatolimab monotherapy) and by visit/sampling timepoint.

2.7.4.1 ECG

Local ECGs are performed at screening, end of treatment and as clinically indicated. If abnormalities are observed based on these local ECGs, these abnormalities are to be reported and thus summarized as AEs.

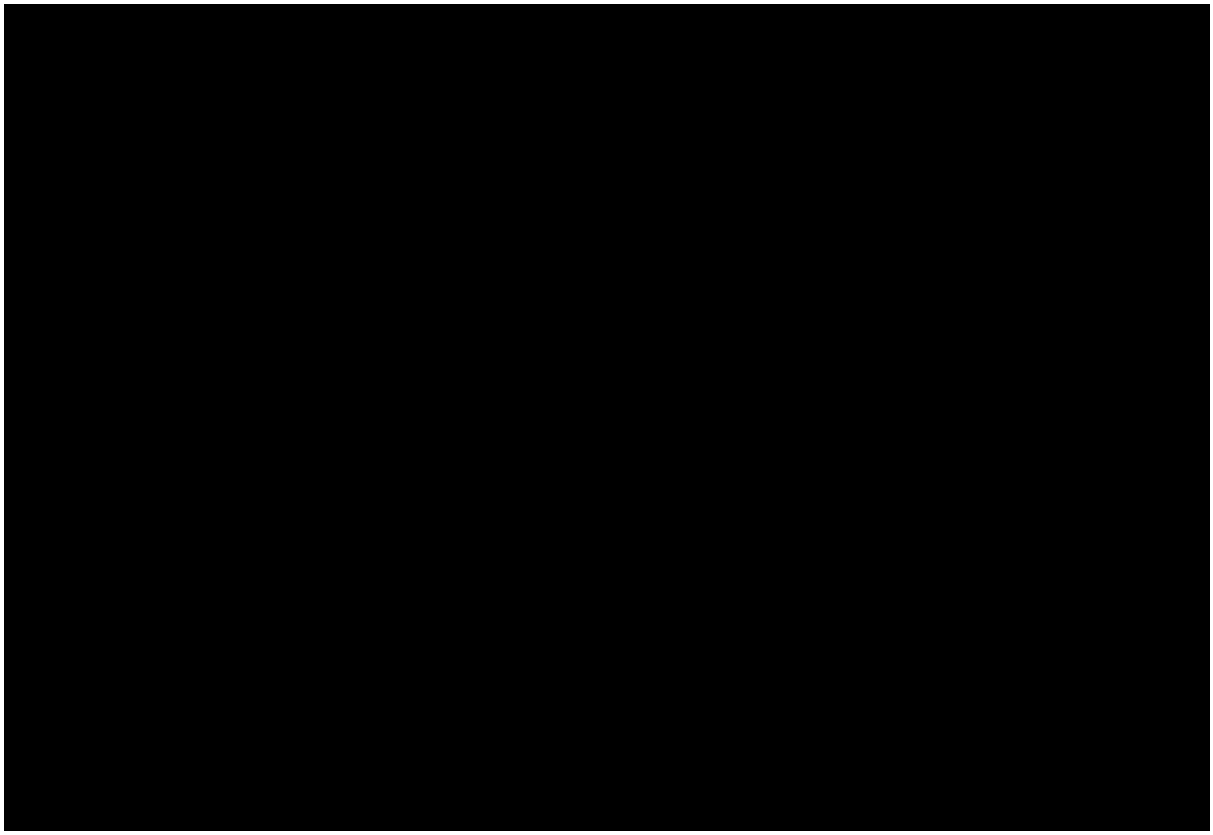
2.7.4.2 Vital signs

Vital sign values during the on-treatment period will be listed.

2.8 Pharmacokinetic endpoints

2.8.1 Sabatolimab drug concentrations

Pharmacokinetic analyses will be summarized for the sabatolimab pharmacokinetic analysis set. Sabatolimab concentration data will be listed by participant, and visit/sampling time point. Descriptive statistics (n, m (number of non-zero concentrations), mean, coefficient of variation (CV%), standard deviation, median, geometric mean, geometric CV%, minimum and maximum) for sabatolimab will be presented at each scheduled timepoint. Below the limit of quantitation (BLQ) values will be set to zero by the Bioanalyst and will be displayed in the listing of all PK concentrations as zero and flagged. However, BLQ values will be treated as missing for the calculation of the geometric means and geometric CV% but included as zero in the other summary statistics. Missing values for PK concentrations will not be imputed and will be treated as missing.



2.10 Interim analysis

Interim analyses are planned for the monitoring of safety data, and will be conducted after each dose level cohort of the safety run-in part to determine the recommended dose for expansion (RDE):

- One meeting after participants included in the first cohort (treated with sabatolimab at the 400 mg Q4W) have completed 2 cycles of treatment,
- A second meeting after participants included in the second cohort (treated with sabatolimab at 800 mg Q4W) have completed 2 cycles of treatment.

The decision to start enrollment in the second cohort and to continue with the sabatolimab dose of 800 mg Q4W in the expansion phase will be guided by a Bayesian analysis based on the incidence of dose limiting toxicity (DLT) data.

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 (including ELN risk category)
- Medical history
- Prior and concomitant medications (including immunosuppressive treatments)
- Participant disposition

- Protocol deviations
- Duration of exposure to study treatment
- Dose intensity and relative dose intensity
- Number (%) of participants with any dose changes (including 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
- AESI overview (if AESI definition is available at the time of the safety review meetings)
- Posterior distribution for the risk of DLT for new participants at the dose level tested (see Section 2.5)
- Laboratory data and vital signs abnormalities
- Investigator's response assessment
- Sabatolimab concentrations (if available)

For the regular safety review meetings conducted after the safety run-in part, the same information as listed above will be provided except the investigator's response assessment as this information is only used for decision making on the RDE.

The exact list of tables, listings and figures prepared for those safety review meetings will be defined in a separate planning document (e.g. TFL).

3 Sample size calculation

Primary safety analysis (incidence of dose-limiting toxicity)

No formal statistical power calculations to determine sample size were performed for the safety run-in part.

A cohort of 6 to 8 participants will be enrolled in the first cohort treated with sabatolimab at 400 mg Q4W dose level and a cohort of 9 to 12 participants will be enrolled in the second cohort treated with sabatolimab at 800 mg Q4W dose level.

In the context of this intrinsic risk of GvHD, the definition of an acceptable level of toxicity does not follow the EWOC criterion (i.e. probability to observe a DLT rate exceeding 33% is below 25%) as defined in a standard oncology Phase I study. Thus, instead of considering a 33% threshold for the probability to observe a DLT rate, 50% will be selected as the threshold to qualify for an acceptable toxicity (i.e. probability to observe a DLT rate exceeding 50% is below 25%).

Data scenarios for the incidence of DLTs in the two cohorts of the safety run-in part, including the decision made based on the dose-DLT Bayesian logistic regression model, as well as operating characteristics, are presented in Appendix 16.6 of the protocol.

Primary efficacy analysis (proportion of participants with no hematologic relapse)

The sample size calculation is based on the proportion of participants reported with no evidence of hematologic relapse (i.e. maintenance of CR or CRi), defined as absence of bone marrow blasts ≥ 5%; absence of reappearance of blasts in the blood; and absence of the development of

extramedullary disease after 6 cycles of treatment. The hypotheses to be tested and details of the testing strategy for each of the study treatment (sabatolimab in monotherapy and sabatolimab in combination with azacitidine) are described in Section 2.5.2.

A sample size of 25 adults, from both the safety-run and expansion monotherapy cohorts treated with sabatolimab in monotherapy at the recommended dose for expansion (RDE), is required to meet both statistical significance (posterior probability that the proportion of adult participants who remain with no evidence of hematologic relapse ≥ 15% is greater or equal to 97.5%) and clinical relevance (posterior probability that the proportion of adult participants who remain with no evidence of hematologic relapse ≥ 30% is greater or equal to 50%). At least 8 participants who remain with no evidence of hematologic relapse after 6 cycles of treatment out of 25 participants treated with sabatolimab in monotherapy are required for success (both statistical significance and clinical relevance met).

A sample size of 20 adult participants treated with sabatolimab in combination with azacitidine (combination cohort) is required to meet both statistical significance (posterior probability that the proportion of participants with no evidence of hematologic relapse ≥ 30% is greater or equal to 97.5%) and clinical relevance (posterior probability that the proportion of participants with no evidence of hematologic relapse ≥ 50% is greater or equal to 50%). At least 11 participants, who remain with no evidence of hematologic relapse after 6 cycles of treatment out of 20 participants treated with sabatolimab in combination with azacitidine, are required for success (both statistical significance and clinical relevance met).

Data scenarios including the decisions for different values of the proportion of participants with no hematologic relapse, as well as operating characteristics, are presented in Section 12.8 of the protocol.

4 Change to protocol specified analyses

Not applicable.

5 Appendix

5.1 General definitions

Date of first administration of study drug (sabatolimab) or azacitidine

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

Date of last administration of study drug (sabatolimab) or azacitidine

The date of the last administration of the study drug (sabatolimab) or azacitidine is defined as the last date when a non-zero dose of the respective study drug or azacitidine 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 cohort)

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

Date of last administration of study treatment (combination cohort)

The date of the last administration of study treatment (or the end 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 or azacitidine) is administered.

Date of last exposure to study drug (sabatolimab) or azacitidine

One planned cycle length is 28 days and the start date of a cycle is defined as the first administration of sabatolimab within a cycle in cohorts when administered in monotherapy (Cohorts 1, 2, 4, and 5) and as the first administration of azacitidine within a cycle in the combination cohort (Cohort 3). Sabatolimab, when administered in monotherapy, is administered every 4 weeks (Q4W), on Day 1 of each cycle, unless there was a toxicity leading to a dosing interval increase. Sabatolimab, when administered in combination with azacitidine, is administered every 4 weeks (Q4W), on Day 5 of each cycle, unless there was a toxicity leading to a dosing interval increase. Azacitidine is planned to be administered daily every cycle during the first 5 days of each cycle (Day 1 to Day 5).

As treatment is given in cycles, the date of the last administration of study treatment is not considered the date of the last exposure but instead the planned end date of the last cycle in which the last non-zero dose was given.

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

- If sabatolimab is given Q4W: Minimum (last date of administration of sabatolimab + 27 days, date of death, last contact date in case participant is lost to follow-up, data cut-off date).

The **date of last exposure to azacitidine** is calculated as:

- Minimum (the last date of administration of azacitidine + 23 days, date of death, the last contact date in case participant is lost to follow-up, data cut-off date) as azacitidine doses are given daily every cycle during 5 days at the beginning of each cycle (between Day1 to Day 5).

The date of last exposure to study treatment (sabatolimab and azacitidine) is defined as:

- The latest date among the last date of exposure to sabatolimab and azacitidine treatment. This date will be taken to derive duration of exposure to study treatment (sabatolimab and azacitidine).

End date of the last cycle initiated

The end date of the last cycle initiated is 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) is administered.

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 cohort)

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

- The date of last exposure to study treatment,
- Date of death,
- Last contact date in case the participant is lost to follow-up.

The duration of exposure to study treatment (combination) will be calculated as follows: 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: date of last exposure - 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).

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, 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 start of study treatment is taken as “baseline” assessment.

If participants have no value as defined above, the baseline result will be missing.

Laboratory parameter derivations

If laboratory values are provided as ‘<X’ (i.e. below limit of detection) or ‘>X’, prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

The following rules will be applied to derive the WBC differential percentages when only absolute differential counts are available for a xxx differential

xxx %value = (xxx count * 100) / WBC count

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, if only serum calcium is collected, the corrected calcium can be derived using the total serum calcium value and serum albumin at the same assessment using the following formula (after values had been converted to SI units):

Corrected Calcium (mmol/L) = Calcium (mmol/L) + 0.02 (40 – [Albumin (g/L)]

For laboratory CTC grade derivations, the normal range for derived corrected calcium is set to the same limits (in mmol/L) as for serum calcium.

6 Reference

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