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Clinical Trial Protocol 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

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List of abbreviations

[redacted]	[redacted]
ADL	Activities of daily living
AE	Adverse Event
aGvHD	acute Graft versus Host Disease
aHSCT	allogeneic Hematopoietic Stem Cell Transplantation
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
AV	Atrioventricular
AZA	Azacitidine
BLRM	Bayesian Logistic Regression Model
BM	Bone marrow
BMA	Bone marrow aspirate
BMB	Bone marrow biopsy
BMT CTN	Blood and Marrow Transplant Clinical Trials Network
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CABG	Coronary artery bypass graft
cGvHD	chronic Graft versus Host Disease
CIBMTR	Center for International Blood and Marrow Transplant Research
CIR	Cumulative incidence of relapse
CK	Creatinine Kinase
Cmax	Maximum plasma concentration
Cmin	Minimum plasma concentration
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CNS	Central nervous system
CO	Country Organization
COA	Clinical Outcome Assessment
COVID-19	Coronavirus disease 2019
CR	Complete remission
CRA	Contract research associate
CRF	Case Report/Record Form (paper or electronic)
CRi	Complete remission with incomplete hematologic recovery
CRO	Contract Research Organization
CRP	C-reactive protein
CSA	Cyclosporin A
CSR	Clinical study report

CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
CTT	Clinical trial team
CV	coefficient of variation
DDE	Direct Data Entry
DDS	Dose determining set
DFS	Disease free survival
DILI	Drug-Induced Liver Injury
DLI	Donor lymphocyte infusion
DLT	Dose Limiting Toxicity
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EFS	Event free survival
ELISA	Enzyme-linked immunosorbent assay
ELN	European Leukemia Network
EMD	Extramedullary disease
EOT	End of treatment
eSource	Electronic Source
EU	European union
EWOC	Escalation with overdose control
FAS	Full Analysis Set
FEV1	Forced expiratory volume in 1 second
FISH	Fluorescence in situ hybridization
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GLDH	Glutamate dehydrogenase
GRFS	GvHD-free/relapse-free survival
GvHD	Graft versus Host Disease
GvL	Graft versus Leukemia
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
Hgb	Hemoglobin
HHV6	Human Herpes Virus 6
HIV	Human immunodeficiency virus
HLA	Human Leukocyte Antigen
HMA	Hypomethylating agent
HR	Hazard ratio
HR-MDS	High-risk myelodysplastic syndrome
hrs	Hour
HSCT	Hematopoietic Stem Cell Transplantation

HSV	Herpes simplex virus
HZV	Herpes Zoster Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IFN	interferon-gamma
[redacted]	[redacted]
IL	Interleukin
IN	Investigator Notification
INR	International Normalized Ratio
IO	Immuno-oncology
iPSP	initial Pediatric Study Plan
irAE	immune-related adverse events
IRB	Institutional Review Board
IRT	Interactive Response Technology
IST	Immunosuppressive treatment
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous
IWG	International Working Group
LAIP	Leukemia associated immunophenotype
LC-MS	Liquid chromatography mass spectrometry
LDH	lactate dehydrogenase
LFS	leukemia-free survival
LFT	Liver function test
LLOQ	lower limit of quantification
LMWH	Low molecular weight heparin
LUC	Large unstained cells
MDRD	Modification of diet in renal disease
MedDRA	Medical dictionary for regulatory activities
MFC	Multiparameter flow cytometry
mg	milligram(s)
MI	Myocardial infarction
mL	milliliter(s)
MLFS	Morphologic leukemia-free state
MRD	Measurable Residual Disease
MUGA	Multiplied-Gated Acquisition
NCI	National Cancer Institute
NGS	Next Generation Sequencing
NIH	National Institutes Health
NK	Natural killer
NTproBNP	N-terminal prohormone brain natriuretic peptide
OS	Overall survival
PB	Peripheral blood
PCR	Polymerase Chain Reaction

PD	Pharmacodynamic
PD-1	Programmed cell death protein 1
PK	Pharmacokinetic(s)
PS	Performance status
Q4W	Every 4 weeks
QMS	Quality Management System
qPCR	Quantitative polymerase chain reaction
QTcF	QT interval corrected by Fridericia's formula
RDE	Recommended dose for expansion
RFS	Relapse free survival
RSV	Respiratory Syncytial Virus
SAE	Serious Adverse Event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous
sCR	serum creatinine
SD	standard deviation
SJS	Stevens-Johnson syndrome
SOP	Standard operating procedures
[redacted]	[redacted]
SUSAR	Suspected Unexpected Serious Adverse Reaction
T3	Triiodothyronine
T4	Thyroxine
TBIL	Total Bilirubin
TEN	Toxic epidermal necrolysis
TIM-3	T-cell immunoglobulin domain and mucin domain-3
TKD	Tyrosine kinase domain
TNF	Tumor necrosis factor
Tregs	T regulatory
TSH	Thyroid-Stimulating Hormone
ULN	upper limit of normal
USA	United States of America
VES	Visit evaluation schedule
VZV	Varicella Zoster Virus
WBC	White Blood Cells
WHO	World Health Organization
WoC	Withdrawal of study Consent
WOCBP	Women of child-bearing potential

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant.
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants.
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)

Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued, and no further assessments are planned
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias
Randomization number	A unique identifier assigned to each randomized participant
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol.
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.

Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

Amendment 2 (24-Mar-2022)

Amendment rationale

At the time of release of this amendment, nine sites have been initiated, twelve patients have been pre-screened and/or screened and four (4) patients have been enrolled into safety run-in cohort 1. One (1) patient is currently receiving study treatment in this trial.

The main purpose of this amendment is to modify some of the inclusion/exclusion criteria that are considered too restrictive and causing slow recruitment rate, per feedback from Principal Investigators on the study. The inclusion/exclusion criteria selected for the amendment were assessed to have no substantial impact on the study design or primary objectives, including safety and preliminary efficacy assessments.

In addition, determination of eligibility for enrollment based on central MRD assay where required (e.g., USA) was added.
Furthermore, format and grammatical corrections as well as removing redundancies are made throughout the protocol to improve flow and consistency.

Changes to the protocol

- Protocol Summary, Section 2.1, Section 3: Updated to allow for MRD positivity window any time at ≥ Day 60 after aHSCT.
- Section 5.1: Updated Inclusion Criteria 4 of eligibility time window based on MRD positivity to [any time at ≥ Day 60 after aHSCT], which will allow earlier eligibility (Day 100 was changed to Day 60) and to remove the Day 365 restriction.
- Section 5.2: Updated Exclusion criteria 8 to allow for participants with history of another malignancy who are receiving adjuvant therapy, such as hormone therapy, to enter the study.
- Section 5.2: Updated Exclusion criteria 18 to allow prior use of "prophylactic" donor lymphocyte infusion (DLI) with or without hypomethylating agent (HMA), if DLI was completed ≥ 3 months and HMA was completed ≥ 4 weeks prior to start of study treatment.
- Section 6.2.2: Added to clarify that DLI and other cellular therapies are prohibited while on study.
- Table 6-2: Modified DLT definition in regard to the duration of grade 4 cytopenias based on FDA feedback.
- Table 6-4: Corrected an error in the lower right cell of the table replacing "grade I" with "mild" for chronic GvHD.
- Section 8.1: Addition of central MRD assessment where required (e.g., USA) and wording modified for more clarity.
- Table 8-1 and Table 8.2: Added DLI and other cellular therapies and updated footnotes for more clarity
- Section 8.2: "Demographics and other baseline characteristics" with the requirement for data collection to capture "prior antineoplastic therapies", prior

to and post-aHSCT, including prior prophylactic DLI(s) with or without hypomethylating agents.

- Table 8-4: Added BMA for MRD by Flow Cytometry unscheduled collection timepoint.
- Section 8.5.3, Table 8-13, Table 8-14: Added Biomarker unscheduled collection timepoint.

IRBs/IECs

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

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

In addition, the changes herein affect the Informed Consent. Sites are required to update and submit for approval the revised Informed Consents, which takes into account the changes described in this amended protocol.

Amendment 1 (16-Apr-2021)

Amendment rationale

At the time of release of this amendment, no sites have been initiated, and no subject has been screened or has received study treatment in this trial.

The main purpose of this amendment is:

- To modify the list of inclusion and exclusion criteria to include requirements for minimum hemoglobin level and restrictions for prior cancer-directed treatments or investigational modalities, and for patient with BCR-ABL mutations eligible for post-transplant tyrosine kinase inhibitor therapies, respectively, as requested by health authorities.
- To provide further clarification on the dose to be used for cohorts 3-5 in the study design schema, how DLTs will be defined and how dose modifications for sabatolimab will be handled, as requested by health authorities.

Other changes include:

- To add/correct visit windows and specify collection of antineoplastic therapies/medications since discontinuation (previously included in collection concomitant medication and therapies) in visit schedule assessments tables

[redacted]

- New Novartis standard language, has been added to update to the most recent version of the Novartis protocol CTP template v4.0

Changes to the protocol

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

- List of Abbreviations / Glossary of Terms: Updated based on changes to the CTP template v4.0
- Section 2 / Section 12.4 / Section 12.4.1 / Section 12.4.3 / Section 12.4.5 / Section 12.5: Updated section title to match CTP template v4.0
- Table 2-1: Rearranged the order of primary objectives to align with the order in which the study cohorts will be conducted
- Figure 3-1: Study design schema was updated to provide further clarification on the dose to be used in cohorts 3-5
- Section 4.6: Updated to include risks and benefits related to COVID-19 vaccination
- Section 5.1: Inclusion criteria #15 for minimum hemoglobin level added
- Section 5.2: Added Exclusion criteria #18 for prior cancer-directed treatments or investigational modalities.

- Section 5.2: Added exclusion criteria #19 for participants with BCR-ABL mutations eligible for post-transplant tyrosine kinase therapies
- Section 6.2.1: Updated to provide a window of when concomitant medication data should be collected.
- Section 6.5.3: Removed text related to DLT definition to provide further clarity
- Table 6-2: Updated DLT criteria in the table to include febrile neutropenia ≥ CTCAE Grade 3 and thrombocytopenia ≥ CTCAE Grade 3 with clinically significant bleeding
- Section 6.5.4: Additional language added to provide further clarity on guidelines for dose modifications for sabatolimab
- Section 7 / Section 9.1.2 / Section 9.1.3 / Section 10.1.3 / Section 10.1.4: Added wording to match CTP template v4.0
- Table 8-1 and Table 8-2: Added visit window +/- 3 days after Cycle 1 Day 1 as stated in Section 8 during the treatment period, added antineoplastic therapy assessment during safety and post-treatment follow-up period.
- Table 8-1 and Table 8-2: Added a check at the screening visit for the collection of the efficacy bone marrow aspirate or biopsy assessment to align with Section 8.3.1.
- Section 8.2: Modified language regarding race/ethnicity baseline characteristics to match CTP template v4.0
- Table 8-11 and Table 8-12: check removed at Day 1 Cycle 24 end of sabatolimab infusion for participants enrolled in monotherapy cohorts (cohorts 1, 2, 4 and 5) and at Day 5 Cycle 24 end of sabatolimab infusion for participants enrolled in combination cohort 3.
- [redacted]

IRBs/IECs

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

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

Protocol summary

Protocol number	CMBG453F12201
Full Title	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.
Brief title	A prospective study of sabatolimab alone or in combination with azacitidine preemptive therapy in patients with acute myeloid leukemia (AML) after allogeneic stem cell transplantation.
Sponsor and Clinical Phase	Novartis Phase Ib/II
Investigation type	Drug: Biological
Study type	Interventional
Purpose and rationale	The primary purpose of this study is to test the hypothesis that preemptive treatment with sabatolimab, alone or in combination with azacitidine, when administered to participants with AML/secondary AML who are in complete remission with positive measurable residual disease post-allogeneic hematopoietic stem cell transplantation (MRD+ post-aHSCT), can enhance the graft versus leukemia (GvL) response and prevent or delay hematologic relapse without an unacceptable level of treatment-emergent toxicities, including clinically significant acute and/or chronic graft-versus-host disease (GvHD) and immune-related adverse events.
Primary Objective(s)	• Safety - for adults only in the Safety Run-in part: to determine whether sabatolimab as monotherapy at the two tested dose levels [400 mg and 800 mg every 4 weeks (Q4W)] leads to an unacceptable level of toxicity when administered post-aHSCT, as measured by the incidence of treatment-emergent dose limiting toxicities (DLTs) during the first 2 cycles of study treatment. • Efficacy- for adults only in both Safety Run-in and expansion parts: to evaluate preliminary efficacy of sabatolimab (at the recommended dose for expansion) as monotherapy and in combination with azacitidine on prevention of hematologic relapse, as measured by the proportion of adult participants with AML and MRD+ post-aHSCT 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). • Safety - for adolescents after completion of the Safety Run-in in adults: 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 post-aHSCT, as measured by the incidence of treatment-emergent dose limiting toxicities during the first 2 cycles of study treatment.
Secondary Objectives	• Incidence of grade III or IV acute GvHD and moderate to severe chronic GvHD. • Pharmacokinetics (PK) of sabatolimab. • GvHD-free/relapse-free survival. • Relapse-Free Survival. • Safety and tolerability of sabatolimab. • Incidence of severe immune-related adverse events not attributed to GvHD.

	• The proportion of participants with centrally confirmed MRD+ at screening who become MRD negative during the first 6 cycles of study treatment.
Study design	This is a phase Ib/II, open label, multi-center study of sabatolimab as monotherapy and in combination with azacitidine, in participants with AML/secondary AML who have received one aHSCT and achieved complete remission but MRD+ any time at ≥ Day 60 after aHSCT and at least 2 weeks after immunosuppressive medications have been tapered off. The study will enroll approximately 59 participants and will be conducted in two parts: Part 1 is a Safety Run-in of approximately 20 participants, to assess whether sabatolimab as monotherapy at the two tested dose levels (400 mg and 800 mg intravenously Q4W) is safe when administered in the post aHSCT setting. 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 (≥ 8 weeks following the first dose). Following the observation period for DLTs, a Safety Review Meeting will be conducted after each dose level to assess safety and determine the recommended dose for expansion to proceed with enrollment of additional cohorts in Part 2 of the study. Part 2 consists of sabatolimab monotherapy expansion cohort of approximately 13 participants, sabatolimab in combination with azacitidine cohort of approximately 20 participants, and an adolescent cohort of approximately 6 participants (≥ 12 years but < 18 years of age) with sabatolimab as monotherapy. Sabatolimab will be administered at the recommended dose for expansion determined in Part 1.
Study population	The study population will enroll approximately 59 participants with de novo AML or secondary AML, who have achieved complete remission after aHSCT and are at high risk for relapse defined by the presence of MRD any time at ≥ Day 60 post-transplant after tapering off immunosuppressive therapy.
Key Inclusion criteria	• At the date of signing the informed consent form (ICF), eligible participants must be ≥ 18 years for the adult cohorts; and ≥ 12 years old but < 18 years old for the adolescent cohort, which will open after completion of Safety Run-in. • Diagnosis of AML/secondary AML and received one prior aHSCT performed to control AML • Participants are eligible irrespective of response or MRD status at time of aHSCT • Participants in complete remission (< 5% bone marrow blasts, absence of circulating blasts in the blood, and no extramedullary disease) with MRD positivity (by local assessment or central assessment where required (e.g. in US)), any time at ≥ Day 60 after aHSCT. • Ability to provide a fresh bone marrow aspirate sample collected within 28 days from enrollment/randomization, and immediately shipped to a Novartis designated central laboratory for MRD testing. • Systemic GvHD prophylaxis or treatment [immunosuppressive treatment (IST)] completely tapered for at least two weeks prior to study entry. Prednisone dose ≤ 5 mg/day or equivalent corticosteroid dose is allowed.

	• Participants who are found with MRD positivity while still on or tapering systemic GvHD prophylaxis or treatment, MRD positivity must be re-confirmed at least 2 weeks after the last dose of IST. • For the adult cohorts, participants must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2. For the adolescent cohort, participants must have a Karnofsky (age ≥ 16 years) or Lansky (age < 16 years) performance status score of ≥ 50%
Key Exclusion criteria	• Prior exposure to TIM-3 directed therapy at any time. • History of severe hypersensitivity reactions to any ingredient of study drug(s) (azacitidine, sabatolimab) or monoclonal antibodies (mAbs) and/or their excipients. • Active acute GvHD grade III-IV [according to Harris et al 2016 criteria (Appendix 1)]. • Active moderate chronic GvHD of the lungs [according to the 2014 NIH consensus criteria (Appendix 2)]. • Active severe chronic GvHD [according to the 2014 NIH consensus criteria (Appendix 2)]. • Active autoimmune disease requiring systemic therapy (e.g. corticosteroids). Topical, inhaled, nasal and ophthalmic steroids are not prohibited. Replacement corticosteroids therapy is allowed and not considered a form of systemic treatment • Live vaccine administered within 30 days prior to the first day of study treatment (C1D1)
Study treatment	Sabatolimab monotherapy Sabatolimab + azacitidine
Efficacy assessments	• Response evaluation will be per Investigator's assessment, based on standardized criteria as proposed by the European LeukemiaNet (ELN) and International Working Group (IWG) for AML (Cheson et al 2003, Döhner et al 2017) • Disease assessment at baseline and evaluation of response during study treatment will rely on bone marrow and peripheral blood assessments. • Disease response (bone marrow assessment, hematology) will be assessed locally at any time as clinically indicated.
Pharmacokinetic assessments	Pharmacokinetic (PK) samples will be obtained and evaluated in all participants.
Key safety assessments	• Acute graft-versus-host disease. • Chronic graft-versus host disease. • Immune-mediated adverse events. • Incidence and severity of adverse events and serious adverse events. • Changes in vital signs. • Changes in laboratory values.
Other assessments	**Biomarker Assessments:** Bone marrow aspirate, peripheral blood and plasma samples will be collected for biomarker assays. These include MRD measurements by multiparameter flow cytometry [redacted]; Samples will be collected at baseline and at regular intervals during the course of the study as defined in the schedule of assessments.

	[redacted]

Data analysis	For adults participants included in the Safety Run-in part of the study, and for the adolescent cohort, the assessment of the acceptable level of toxicity with sabatolimab in monotherapy will be guided by a Bayesian Logistic Regression Model (BLRM). The probability that the true Dose Limiting Toxicity (DLT) rate exceeds 50% should be lower than 25% to declare that sabatolimab in monotherapy is reaching an acceptable level of toxicity.
	
	Efficacy of sabatolimab will be assessed based on the proportion of adult participants treated with sabatolimab at the recommended dose for expansion, as monotherapy or in combination with azacitidine, who remain with no evidence of hematologic relapse after 6 cycles of study treatment as per investigator assessment and using a Bayesian dual-criterion design:
	• Adult participants treated with sabatolimab monotherapy: At least 8 participants with no evidence of hematologic relapse after 6 cycles of treatment out of 25 participants are required for success
	  • 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 ≥ 15% is at least 97.5% (statistical significance at 2.5% level, 1-sided)
	  • Clinical decision rule: the posterior median for the proportion of adult participants who remain with no evidence of hematologic relapse is ≥ 30%.
	• Adult participants treated with sabatolimab in combination with azacitidine: At least 11 participants with no evidence of hematologic relapse after 6 cycles of treatment out of 20 participants are required for success
	  • 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 ≥ 30% is at least 97.5% (statistical significance at 2.5% level, 1-sided)
	  • Clinical decision rule: the posterior median for the proportion of adult participants who remain with no evidence of hematologic relapse is ≥ 50%.

Key words	Phase Ib/II, sabatolimab, TIM-3, azacitidine, Acute Myeloid Leukemia, allogeneic hematopoietic stem cell transplantation, measurable residual disease.

1 Introduction

1.1 Background

Acute myeloid leukemia, allogeneic hematopoietic stem cell transplantation and graft-versus-host disease / graft-versus-leukemia:

Acute myeloid leukemia (AML) is a malignant disease characterized by the clonal expansion of myeloid blasts in the bone marrow, peripheral blood and extramedullary tissues. AML is the most common form of acute leukemia in adults; an estimated 21,450 new cases of AML and 10,920 deaths from the disease will occur in the United States, in 2019 (American Cancer Society 2019). Intensive chemotherapy is standard of care for first line treatment, which achieves complete remission (CR) in a majority of cases; however, most participants will experience relapse without additional therapy. Post-remission allogeneic hematopoietic stem cell transplantation (aHSCT) is the only curative treatment for most participants with AML.

aHSCT is a potentially curative treatment for AML. The anti-leukemia effect of aHSCT depends on the cytotoxicity of the pretransplant conditioning therapy and the posttransplant graft-versus-leukemia (GvL) effect (Dickinson et al 2017).

However, clinically significant acute and chronic graft-versus-host disease (GvHD) occur following aHSCT, with reported incidence rates ranging from 9% to 50% for acute GvHD (aGvHD) and from 30% to 70% for chronic GvHD (cGvHD) (Jagasia et al 2012, Lee et al 2013) (Flowers et al 2002, Lee and Flowers 2008, Flowers et al 2011, Flowers and Martin 2015, Jagasia et al 2015, Vaughn et al 2015).

The incidence of GvHD varies based on several factors, including but not limited to degree of human leukocyte antigen (HLA) matching between the donor and recipient, graft source, conditioning regimen, and GvHD prophylaxis.

GvHD remains a serious and common complication, contributing to post-aHSCT morbidity and mortality. However, a retrospective analysis of data reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) registry on 2905 participants who developed grade II-IV aGvHD following aHSCT for hematological malignancies (56% AML) between 1999 and 2012, demonstrated a shift in maximal grade of aGvHD and a decrease in the proportion of grade III-IV disease over time [56%, 47%, and 37% for 1999-2001, 2002-2005, and 2006-2012, respectively]. In addition, the overall survival and treatment related mortality improved significantly overtime with a decline in deaths from organ failure and infection (Khoury et al 2017).

Notably, analysis of the impact of cGvHD and its severity indicates a close relationship between cGvHD and the immune-mediated GvL effect; as demonstrated with a lower risk of relapse translating into improved disease free survival (DFS) with mild or moderate cGvHD compared to no cGvHD (Mo et al 2015).

Relapse post-aHSCT:

Unfortunately, 30-40% of participants with AML will relapse after transplant and this is the major cause of treatment failure (Thekkudan et al 2020). The outcomes for participants relapsing after aHSCT are poor with limited therapeutic options and no standard of care. Bejanyan et al. published the outcome data reported to the CIBMTR from 1788 participants (age range, <1 to 76 years) with AML who relapsed after aHSCT during first or second complete remission/response (CR). Median time to post-aHSCT relapse was 7 months

(range, 1 to 177). Relapses post-aHSCT occurred within <6 months in 43% of participants, between 6 months-2 years in 39%, between 2-3 years in 8%, and within ≥ 3 years post-aHSCT in 10%. At relapse, participants received intensive therapy, including chemotherapy alone, donor lymphocyte infusion (DLI) +/- chemotherapy, or second aHSCT +/- chemotherapy +/- DLI, with subsequent CR rates of 29%. Survival for all participants was 23% at 1 year after relapse; however, 3-year overall survival (OS) correlated with time from aHSCT to relapse with dismal survival with early disease relapse post-aHSCT (4% for relapse during the 1- to 6-month period, 12% during the 6-month to 2-year period, 26% during the 2- to 3-year period, and 38% for ≥3 years) (Bejanyan et al 2015).

Measurable residual disease (MRD) post-aHSCT and relapse:

Several studies reported that detection of MRD post-aHSCT [by multiparameter flow cytometry (MFC), polymerase chain reaction (PCR), next generation sequencing (NGS), levels of mixed chimerism (as a surrogate), interphase fluorescence in situ hybridization (FISH) or conventional cytogenetics] identifies participants at high risk for subsequent relapse, poor outcome and survival. (Fang et al 2012, Appelbaum 2013, Campana and Leung 2013, Hourigan and Karp 2013, Zhou et al 2016, Liu et al 2019, Thol et al 2019).

Liu et al. retrospectively reported the relationship between MRD by multicolor flow cytometry and transplant outcomes in 460 participants with AML who received haploidentical aHSCT in first or second complete remission. Compared to participants with negative MRD post-aHSCT, participants with detectable MRD+ post-aHSCT had statistically significantly higher cumulative incidence of relapse (100.0% vs 8.3%), lower 3-year probabilities of overall survival (OS) (16.9% vs 78.2%) and leukemia-free survival (LFS) (0% vs 76.5%). These results indicate that MRD assessment may be useful for risk stratification (Liu et al 2019).

Thol et al. also reported on the prognostic impact of MRD by next generation sequencing (NGS) in participants with AML who achieved complete remission following aHSCT, using peripheral blood samples in the majority of the analyses. MRD positivity by NGS on day 90 and/or day 180 post-aHSCT was detected in 16% and 20.3% of participants with the limited (1-2 markers per patient) and extended (2-4 markers per patient) marker approach, respectively. MRD by NGS was predictive for cumulative incidence of relapse (CIR) (58% in for participants with MRD+ and 27% with MRD negative with the extended marker approach) and OS; which remained significant in multivariate analysis for CIR (HR 4.75; CI 2.66-8.50; P=<0.001) and OS (HR 2.56; CI 1.26-5.20; P<0.009) (Thol et al 2019).

TIM-3 blockade and sabatolimab:

T-cell immunoglobulin and mucin domain-containing 3 (TIM-3; also known as hepatitis A virus cellular receptor 2) has a widespread and complex role in immune system regulation, with published roles in both the adaptive immune responses (CD4+ and CD8+ T effector cells, regulatory T cells) and innate immune responses (macrophages, dendritic cells, NK cells). TIM-3 was initially described as an inhibitory protein expressed on activated T helper (Th) 1 CD4+ and cytotoxic CD8+ T cells that secrete interferon-gamma (IFN-γ) (Monney et al 2002, Sánchez-Fueyo et al 2003). TIM-3 is enriched on FoxP3+ Tregs and constitutively expressed on DCs, monocytes/macrophages, and NK cells (Anderson et al 2007, Ndhlovu et al 2012). Further, TIM-3 has also been identified as an acute myeloid leukemia (AML) stem cell antigen that is present in leukemic blasts but not normal hematopoietic stem cells, and anti-TIM-3 antibody treatment has shown efficacy in blocking engraftment of AML in a mouse xenotransplantation model

(Kikushige et al 2010). Promising preclinical and clinical anti-cancer activity has been reported for TIM-3 blockade (Kikushige et al 2010, Sakuishi et al 2010, Ngiow et al 2011, Sakuishi et al 2011, Jing et al 2015, Asayama et al 2017).

Sabatolimab, a novel monoclonal antibody inhibitor of TIM-3, has shown preliminary evidence of clinical activity as a single-agent in participants with relapsed/refractory AML, and promising evidence of efficacy, including durable CRs of up to 24 months, when administered in combination with HMAs to participants with newly diagnosed AML and high-risk MDS.

Immunomodulation and enhancement of GvL:

Immunomodulatory agents and/or checkpoint inhibitors, including sabatolimab, may represent an effective maintenance or preemptive intervention to prevent or delay hematological relapse in the post-aHSCT by enhancing GvL effect and potentially restoring/improving immune surveillance and destruction of malignant cells by alloreactive donor T cells. However, interventions aiming at enhancing GvL effect of the allogeneic graft may be associated with increased risk or worsening of acute and chronic GvHD, which are major causes of non-relapse mortality after aHSCT.

Therefore, a sabatolimab-mediated enhancement of GvL could potentially exacerbate GvHD, an immune-mediated toxicity and a principal safety concern in the aHSCT setting. There are no reported data on the safety of sabatolimab in the post-aHSCT setting. However, preliminary available data on sabatolimab-associated irAEs appear to be limited and less frequent compared to PD-1 blockade.

Recent report on 15 participants treated with sabatolimab in combination with HMA for MDS and AML successfully proceeded to aHSCT within a median of 29 days (range 10-145 days) from the last dose of sabatolimab until transplant. No sabatolimab was administered post-aHSCT. Limited toxicities related to GVHD were reported [6 participants with grade I-II acute GVHD (skin, n=6; upper GI, n=1), no grade III or higher GVHD and 3 participants with chronic GVHD: 2 had liver involvement, both responsive to steroids, and one had ocular and oral cGVHD] (Brunner et al 2020).

Azacitidine:

Azacitidine (AZA), a pyrimidine analog and HMA, with antineoplastic effects. Azacitidine has been shown to have effects on the activation and proliferation of T cells suggesting a role in GVL and GVHD. AZA and other HMAs, upregulate silenced minor histocompatibility and tumor antigens on leukemic blasts, potentially augmenting the GVL response. It is also noted that azacitidine facilitates T regulatory cell (Tregs) reconstitution, which may reduce GVHD risk.

The safety of azacitidine at 75 mg/m2 SC or IV x 7 days of every 28-day cycle in combination with sabatolimab at 800 mg IV Q4W has been evaluated in MDS and AML population and found to be safe and tolerable.

Azacitidine is not yet approved in the post aHSCT setting. However, azacitidine has been tested at different doses and schedules in various clinical studies in the post-aHSCT setting as preemptive or maintenance therapy of AML or MDS (Thekkudan et al 2020).

A dose and schedule finding study of azacitidine was conducted by de Lima et al (de Lima et al 2010) with different dose levels (8, 16, 24, 32, or 40 mg/m2) for 5 days for one to four 30-day cycles, in 45 participants with high-risk MDS/AML starting from the sixth week after aHSCT. The dose of 32 mg/m2 was chosen as optimal, as further dose

escalation was limited by thrombocytopenia. Their results suggested that azacitidine may prolong event-free survival (EFS) and overall survival (OS). However, there was no significant association between the azacitidine dose and OS or EFS.

In addition, the RICAZA phase I/II study (Craddock et al 2016, Goodyear et al 2012) analyzed the impact of maintenance with azacitidine at a dose of 36 mg/m2 SC for 5 days, every 28 days, starting on day+ 42 post-aHSCT [median of 54 days (range, 40 to 194 days)], for up to 1 year post-aHSCT in participants with AML (n=37). Azacitidine was well-tolerated in the majority of participants. The 1-year and 2-year relapse-free survival (RFS) were 57% and 49%, respectively. Induction of CD8+ T cell response to tumor antigens, one of the proposed mechanisms of graft-vs-leukemia (GvL) augmentation by azacitidine, was associated with a reduced risk of disease relapse (hazard ratio 0.30; 95% confidence interval [CI], 0.10 to 0.85; P= 0.02) and improved relapse-free survival (HR, 0.29; 95% CI, 0.10 to 0.83; P= 0.02). This GvL augmentation was not associated with increased risk of GvHD, likely due to azacitidine-induced T regulatory cell expansion. Of interest, the dose of azacitidine observed to induce a CD8+ T cell response in this study is approximately one-half that utilized in the treatment of participants with de novo AML or MDS, consistent with the hypothesis that the observed reduction in relapse is consequent upon manipulation of the alloreactive response and maybe achieved with low doses of azacitidine.

The phase II RELAZA trial (Platzbecker et al 2012, Platzbecker et al 2018) reported on 20 participants treated with preemptive azacitidine for decreasing CD34 cell chimerism, at a dose of 75 mg/m2/day SC, for 7 days, for 4 cycles every 28 days while still in complete remission post-aHCST. About 80% (16/20) of participants had either increasing CD34+ donor chimerism to ≥80% or stabilization of chimerism, in the absence of relapse. In those who ultimately relapsed (13 participants, 65%), there was a considerable 7-month delay after initial decrease of CD34 donor chimerism to <80%. However, grade 3-4 neutropenia and thrombocytopenia were common.

Additional data were reported with the RELAZA2 phase II study (Platzbecker et al 2018) in 53 participants with advanced MDS or AML, who had achieved a complete remission after conventional chemotherapy (n= 29) or after aHSCT (n= 24), and treated with azacitidine preemptively when presented with a detectable minimal residual disease (MRD) by quantitative PCR for mutant NPM1, leukemia-specific fusion genes (DEK–NUP214, RUNX1–RUNX1T1, CBFb–MYH11), or by decreasing CD34 cell chimerism after aHSCT. The azacitidine dose was 75 mg/m2 per day SC for 7 days of a 29-day cycle for 24 cycles. After 6 cycles, participants with MRD negativity responses were eligible for a treatment de-escalation. Of the 24 participant post-aHSCT, 17 participants (71%) were relapse-free and alive 6 months after the start of azacitidine and 7 participants had no response. At the data cutoff, 12 of the 17 responding participants were alive and in ongoing remission. Among all treated participants, the most common (grade 3–4) adverse event was neutropenia, occurring in 45 (85%) of 53 participants. One participant with neutropenia died because of an infection considered possibly related to study treatment.

Therefore, the dual activity of azacitidine as an antileukemic agent and inhibitor of GvHD, and the availability of published data on the use of azacitidine in the post-aHSCT setting, make it an attractive partner for combination with sabatolimab post-aHSCT to mitigate the potential risk of inducing or worsening of GvHD.

1.2 Purpose

The primary purpose of the current study is to test the hypothesis that preemptive treatment with sabatolimab, alone or in combination with azacitidine, when administered to participants with AML/secondary AML who are in complete remission with MRD+ post-aHSCT, can enhance the GvL response and prevent or delay hematologic relapse [ie, maintenance of complete remission (CR) or CR with incomplete hematologic recovery (CRi) without development of hematologic relapse (no evidence of bone marrow blasts ≥5%; no evidence of reappearance of blasts in the blood; no evidence development of extramedullary disease) after 6 cycles of study treatment].

MRD for participant selection and enrichment:

Despite the challenges in standardizing definitions of assay-specific and AML-specific thresholds of MRD and the lack of one universal modality or target, there is now evidence that MRD monitoring can improve relapse risk stratification and detection in AML (Hourigan and Karp 2013, Schuurhuis et al 2018a), and see Section 1.1 MRD post-aHSCT and relapse.

MRD positivity post-aHSCT identifies patients at high risk for subsequent relapse, poor outcome and survival (See Section 1.1). Therefore, positive MRD may serve as a predictor for disease recurrence, enrich for trial population and provide a setting to test various post transplantation preemptive therapies in patients with AML post-aHSCT. Harnessing the immune system to enhance the GvL effect is one of the intervention aim in the setting of post-aHSCT with MRD+.

Safety Run-in of sabatolimab monotherapy:

A sabatolimab-mediated enhancement of GvL could potentially exacerbate GvHD, an immune-mediated toxicity and constitutes the principal safety concern in the post-aHSCT setting. There are no reported data on the safety of sabatolimab in the post-aHSCT setting; therefore, an important safety objective will be to assess the occurrence and severity of treatment-emergent aGvHD and cGvHD, immune-related and other adverse events.

The study will start with a Safety Run-in to assess whether sabatolimab can be administered in the post-aHSCT setting without unacceptable levels of treatment-emergent toxicities (dose limiting toxicities, ie; primary safety objective), including increased or worsening risk of treatment emergent aGvHD or cGvHD, as well as severe immune-related toxicity during the first2 cycles of study treatment. The Safety Run-in will be conducted starting with a lower MBG453 dose (ie, 400 mg IV Q4W) than what is currently being used in the MDS and AML setting outside of aHSCT setting (ie, 800 mg IV Q4W). If unacceptable toxicities are not observed, a new cohort of participants treated at 800 mg IV Q4W will subsequently be evaluated.

Details on dose escalation guidelines and determination of the recommended dose for expansion are provided in Section 6.5.

Sabatolimab will then be evaluated at the recommended dose for expansion during Safety Run-in as monotherapy as well as in combination with azacitidine.

Combination with azacitidine:

Azacitidine is not yet approved in the post aHSCT setting, however, it has been tested at different doses and schedules in various clinical studies in the post-aHSCT setting as preemptive or maintenance therapy of AML or MDS (See Section 1.1). Based on the

available published data on the safety and efficacy of various dosing regimens of azacitidine in the post-aHSCT setting, lower doses of azacitidine were selected (50 mg/m2 SC x 5 days of every 28-day cycle) aiming to improve the tolerability of treatment with likely less hematological toxicities and infectious complications after aHSCT; enhance the adherence to treatment schedule and protocol compliance by reducing the burden of frequent hospital visits; and increase the likelihood of a greater efficacy with the an administration of more cycles of azacitidine. For further details, please see Section 1.1.

The dual activity of azacitidine as an antileukemic agent and inhibitor of GvHD, and the availability of published data on the use of azacitidine in the post-aHSCT setting, make it an attractive partner for combination with sabatolimab post-aHSCT to mitigate the potential risk of inducing or worsening of GvHD.

Adolescent cohort:

In addition to the adult cohorts, a cohort of approximately 6 adolescent participants who are ≥ 12 years old but <18 years old and meet eligibility for this study will be enrolled. Data (PK, safety and preliminary response assessment) obtained from adults and the additional cohort of adolescent participants in this study will be used to inform the design and doses for the evaluation of the initial pediatric study plan (iPSP) through modelling and simulation.

2 Objectives, endpoints and estimands

All secondary [redacted] objectives will be applicable in adult and adolescent participants separately, unless otherwise specified.

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• 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.
• 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,) 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).
• For adolescents only: To determine whether sabatolimab as monotherapy at the recommended dose level for adults leads to an unacceptable level of toxicity when	• Incidence of treatment-emergent dose limiting toxicities (DLTs), including aGvHD and cGvHD during the first 2 cycles of study treatment.

Objective(s)	Endpoint(s)
administered to adolescent participants with AML who are in complete remission but are MRD+ post-aHSCT.	
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.
• 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.
• 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.
• 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.
• 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.
• 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.
• 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 (see Section 8.3.2).
[redacted]	

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+?
- Efficacy: What is the effect of sabatolimab at the RDE, as monotherapy and in combination with azacitidine, on prevention of hematologic relapse (ie, 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) after aHSCT regardless of treatment interruption or discontinuation during study and until use of donor lymphocyte infusion (DLI) 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+?

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 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 (minimum exposure criterion defined in 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 dose limiting toxicity (DLT) (see Table 6-2) 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 estimands 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 after 6 cycles of the 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 remaining 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).
- 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 as a responder (treatment policy strategy).
- Start of donor leucocytes 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).

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 treatments 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 in monotherapy or sabatolimab in combination with azacitidine) meets both statistical and clinical significance (Section 12.4.2).

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 (minimum exposure criterion defined in Section 12.1) or who experienced a DLT within the DLT observation period.
2. Primary variable: Proportion of adolescent participants who experience at least one dose limiting toxicity (DLT) (see Table 6-2) 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.

2.2 Secondary estimands

Not applicable.

3 Study design

This is a Phase Ib/II open label, multi-center 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 CR (bone marrow blasts < 5% and no extramedullary disease) but MRD+, any time at ≥ Day 60 after aHSCT (MRD positivity confirmed at least 2 weeks after immunosuppressive medications tapered off).

Study treatment will be administered in 28-day treatment cycles. The study will enroll a total of approximately 59 participants [20 participants in safety run-in (Cohorts 1 and 2), 13 in sabatolimab monotherapy expansion cohort (Cohort 4), 20 in the combination cohort (Cohort 3), 6 in the adolescent cohort (Cohort 5)] and will be conducted in two parts (Figure 3-1).

Part 1 is a Safety Run-in to assess whether sabatolimab is safe in the post-aHSCT setting when administered as a single agent at two dose levels, 400 mg and 800 mg, on a Q4W regimen on Day 1 of every 28-day cycle. Sabatolimab has been demonstrated to be safe and well tolerated as a single agent and in combination with HMAs in previous studies. However, sabatolimab has not been explored in the post-aHSCT setting; therefore, the principal assessment of safety will be based on the rate of unacceptable level of toxicity [ie, treatment-emergent dose limiting toxicities (DLTs) including but not limited to aGvHD and cGvHD] during the first 2 cycles of study treatment (Table 6-2).

A total of approximately 20 participants will be enrolled to Part 1 across the two dose levels. Approximately 8 participants will be enrolled at the starting dose level, 400 mg Q4W IV in order to obtain at least 6 evaluable participants. If the observed DLTs rate does not exceed the acceptable threshold at this starting dose, then approximately 12 participants will be enrolled in a second cohort of Safety Run-in and treated with sabatolimab monotherapy at dose level 800 mg Q4W in order to obtain at least 9 evaluable participants. 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 (≥ 56 days following the first dose) (Section 6.5.3). If no safety concerns were identified at either sabatolimab dose level, the preferred dose level for sabatolimab will be 800 mg IV Q4W.

Part 2 will assess efficacy as well as safety, PK, and MRD status when sabatolimab is administered at the recommended dose for expansion determined in Part 1 as monotherapy and/or in combination with azacitidine. Part 2 will enroll a total of approximately 13 participants in the monotherapy expansion [to obtain a total of 25 participants from the combined Safety Run-in (Cohort 2) and monotherapy expansion cohort (Cohort 4)]; and 20 participants in the combination cohort (Cohort 3). Participants will be randomized to one of these two cohorts in Part 2 - combination cohort (Cohort 3) or monotherapy expansion cohort (Cohort 4) - and the randomization ratio will depend on the number of participants from the Safety-Run in part (Part 1) already treated with sabatolimab at the selected dose level for expansion (See Section 6.3.2).

In the monotherapy expansion cohort (Cohort 4), sabatolimab will be administered as a single agent on Day 1 (Q4W) of every 28-day cycle.

In the combination cohort (Cohort 3) of sabatolimab with azacitidine, sabatolimab will be administered on Day 5 (+3 days) of every 28-day cycle IV on a Q4W regimen.

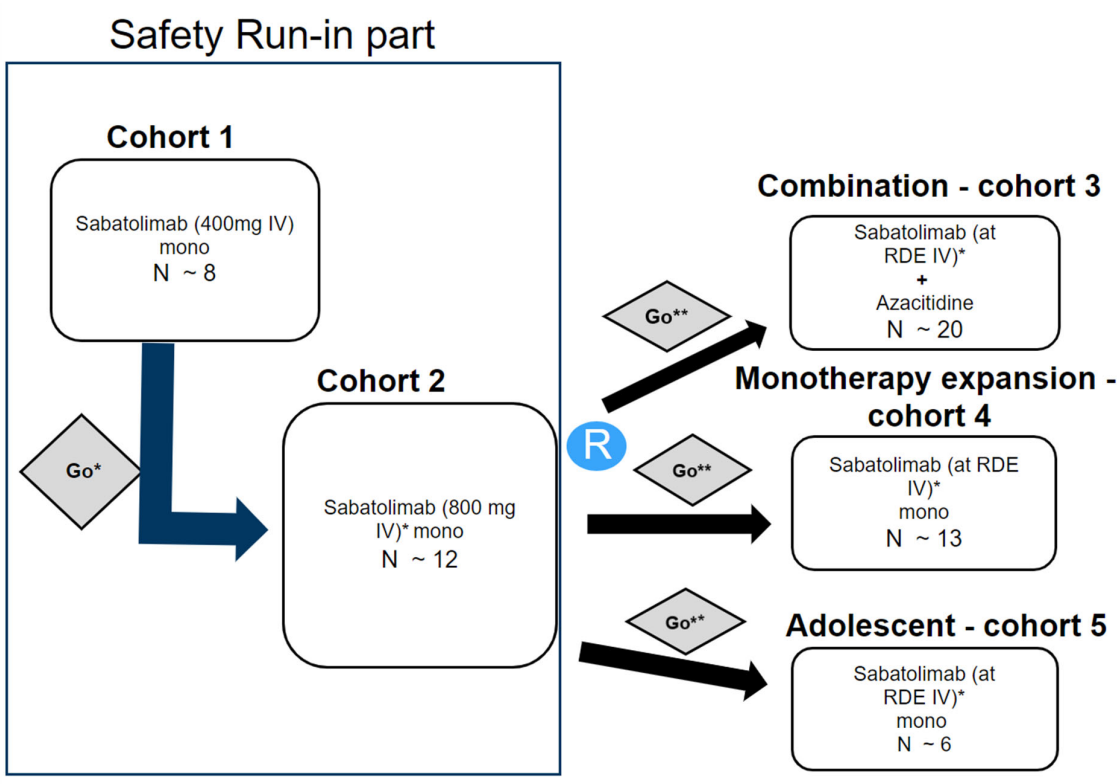
Azacitidine will be administered IV or SC at 50 mg/m^2 on Days 1 to 5 for 5 days per cycle. In the combination cohort (Cohort 3), participants unable to tolerate one of the study drugs may continue on study receiving only the tolerated study drug.

In addition, based on Part 1 Safety Run-in results, an additional cohort of 6 adolescent participants (Cohort 5) will be opened (if no unacceptable rate of toxicities is observed in adults) to include participants who are 12 years or older but less than 18 years old and meet eligibility for this study. This cohort will be conducted in aHSCT site(s) that treat participants at this age group**.**

The decision to open the combination cohort (Cohort 3) and the adolescent cohort (Cohort 5) will be based principally on safety data obtained in Part 1. The decision to open the sabatolimab monotherapy expansion cohort (Cohort 4) will be based on an overall assessment of available safety, preliminary response assessment, PK, and MRD assessments.

Throughout the study, the decision whether or when to open an additional cohort(s) will be based on the overall safety, PK, tolerability, and preliminary response assessment.

Figure 3-1 Study design



* Criteria to proceed with sabatolimab dose increase or Go/No Go for Cohort 2: based on DLTs during the first 2 cycles of study treatment in Cohort 1.
** Go criteria for potential expansion monotherapy cohort, combination cohort and adolescent cohort at the recommended dose for expansion determined by Safety Run-in: Based on an overall assessment of all available data, including safety, preliminary response assessment, clinical pharmacology, tolerability, and recommendations from participating investigators
R: participants will be randomized to Cohort 3 or Cohort 4

Study treatment will be administered for up to a maximum of 24 cycles or until a participant experiences hematologic relapse (bone marrow blasts ≥5%; or reappearance of blasts in the blood; or development of extramedullary disease) as defined by ELN 2017 (Döhner et al 2017); or unacceptable toxicity, whichever is earlier. For participants who achieve negative MRD and maintain MRD negativity for 12 consecutive cycles, study treatment (sabatolimab monotherapy or sabatolimab in combination with azacitidine) may be discontinued earlier at investigator's discretion.

In each cohort, response status will be evaluated by standard hematologic/morphologic criteria per investigator's assessment after each cycle up to Cycle 3, then after every 3 cycles of study treatment up to cycle 12, and then after every 6 cycles for up to a total of 24 cycles (post cycle 1, 2, 3, 6, 9, 12, 18, 24).

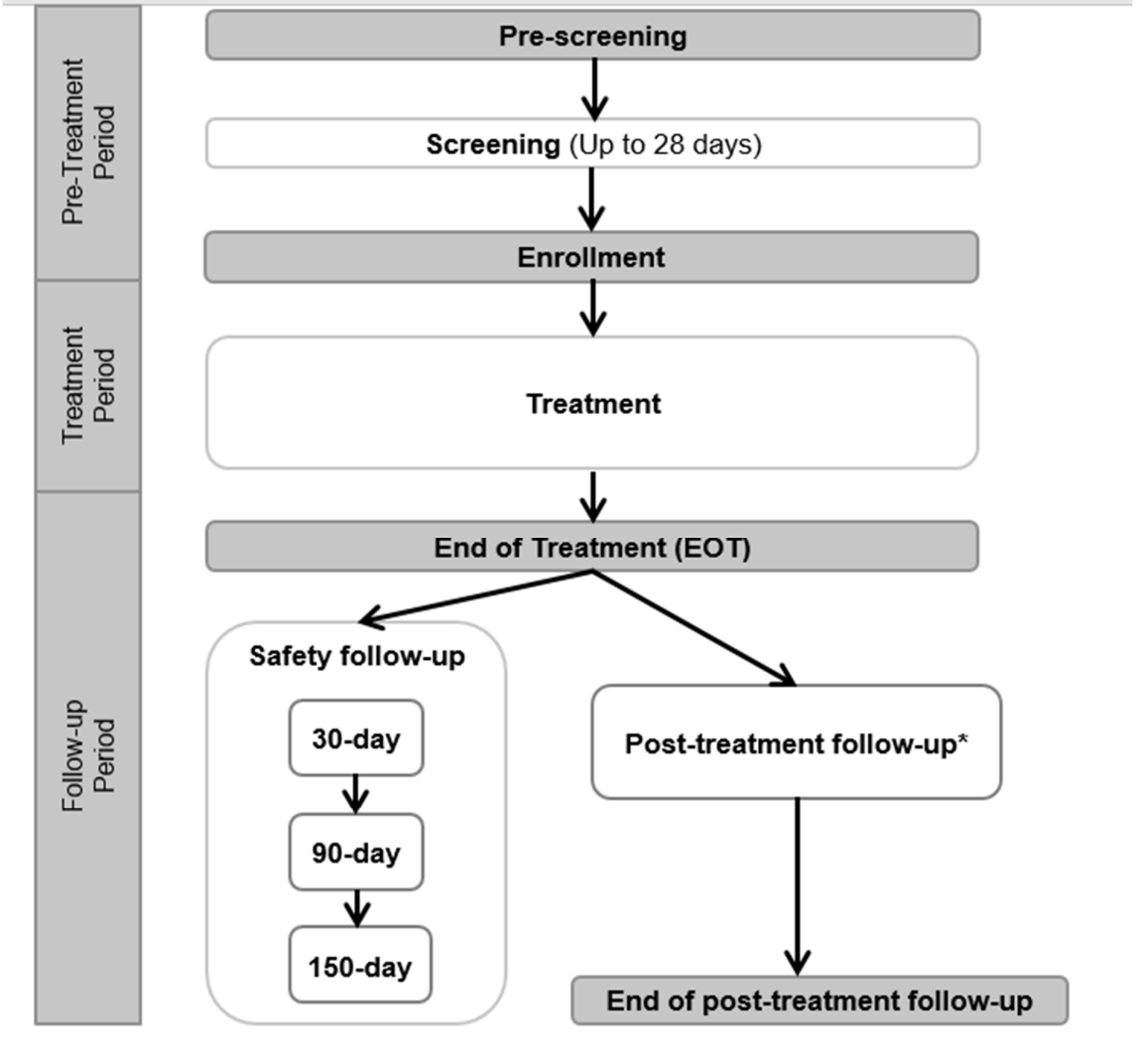
For participants with MRD+ centrally assessed at baseline (defined as at time of enrollment prior to starting treatment), MRD status will be evaluated by Novartis central laboratory at the same schedule as the hematologic/morphologic disease assessment after cycles 1, 2 and 3 and then after every 3 cycles of study treatment up to cycle 12, and then after every 6 cycles for up to a total of 24 cycles (post cycle 1, 2, 3, 6, 9, 12, 18, 24). In addition, MRD status will be assessed locally at the same schedule as the hematologic/morphologic disease assessment after cycles 1, 2 and 3 and then after every 3 cycles of study treatment up to cycle 12, and then after every 6 cycles for up to a total of 24 cycles (post cycle 1, 2, 3, 6, 9, 12, 18, 24).

After completion of the treatment period, all participants will enter post-treatment follow-up until hematologic relapse or start of new therapy. [redacted]

After the end of study treatment, all participants must be followed for adverse events (AEs) for 150 days following the last dose of sabatolimab, or 30 days following the last dose of azacitidine, whichever is later. All participants who discontinued study treatment while in remission with absence of hematologic relapse will enter a long-term follow-up for efficacy as described in the study flow diagram below (Figure 3-2) and outlined in Section 9.1.

Study flow

Figure 3-2 Study Flow



*All participants will enter safety follow-up. After completion of the treatment period, all participants who discontinued study treatment while in remission with no evidence of hematologic relapse will enter post-treatment follow-up until hematologic relapse or start of new therapy. Additionally, participants with MRD- status at end of treatment will continue to be assessed for MRD until MRD+ or for 12 months after end of study treatment, whichever is earlier.

The study flow is comprised of 4 periods (Figure 3-2): prescreening, pretreatment (Screening), treatment, and follow up.

Participants will undergo safety assessments during screening and periodically during treatment and follow-up as outlined in Table 8-1 and Table 8-2.

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

Based on safety and efficacy in previous cohorts, option, via protocol amendment, for expansion cohorts or additional treatment cohorts combining sabatolimab with e.g. donor lymphocyte infusions (DLI) or other novel combinations will be considered.

4 Rationale

4.1 Rationale for study design

The rationale for the design of this phase Ib/II, multicenter, open-label, proof-of-concept study is to assess the safety and preliminary efficacy of sabatolimab monotherapy and sabatolimab combination with azacitidine for preventing/delaying disease relapse in participants with AML/secondary AML post-aHSCT who achieved complete remission but with MRD positivity, indicating increased risk for disease relapse.

A sabatolimab-mediated enhancement of GvL could potentially exacerbate GvHD and immune-related adverse events, therefore, the study employs a 2-part Safety Run-in to assess whether sabatolimab is safe at two dose levels with a halt between cohort 1 (at 400 mg Q4W) and cohort 2 (at 800 mg Q4W) prior to dose escalation and a Safety Review Meeting at each dose level. The occurrence and severity of treatment-emergent aGvHD and cGvHD, immune-related and other adverse drug reactions on sabatolimab as monotherapy post-aHSCT after the completion of at least 2 cycles of study treatment will be assessed. As the start of GvHD and/or immune-related adverse events induced by immunomodulatory agents and/or checkpoint inhibitors, may be delayed, a minimum of 2 cycles with at least 8 weeks following the first dose of sabatolimab was designated.

The timing of efficacy assessment, as measured by the proportion of adult participants who remain with no evidence of hematologic relapse (no evidence of bone marrow blasts ≥5%; no evidence of reappearance of blasts in the blood; no evidence development of extramedullary disease) after 6 cycles of the study treatment, is based on the reported timing of AML hematologic relapse post-aHSCT (median time to relapse 7 months (range, 1 to 177), with 43% of relapses within <6 months). For details, refer to Background Section 1.1 (Bejanyan et al 2015).

The study treatment will be open-label without blinding as this is a proof-of-concept study in participant population at high risk for relapse. However, in Part 2 of the study, participants will be randomized to be enrolled in either the combination cohort (Cohort 3) or the monotherapy expansion cohort (Cohort 4) to minimize selection bias.

Rationale for inclusion of the adolescent cohort: In addition to data obtained from adult participants (PK, safety and preliminary response assessment), enrollment of the adolescent cohort will enable obtaining additional information from this age group to inform the design and doses for the evaluation of the initial pediatric study plan (iPSP) through modelling and simulation.

4.2 Rationale for dose/regimen and duration of treatment

Immunomodulatory agents and/or checkpoint inhibitors may represent an effective maintenance or preemptive intervention to prevent or delay hematological relapse in the post-aHSCT by enhancing GvL effect and potentially restoring/improving immune surveillance and destruction of malignant cells by alloreactive donor T cells (Thekkudan et al 2020). However, interventions aiming at enhancing GvL effect of the

allogeneic graft may be associated with increased risk or worsening of acute and chronic GvHD, which are major causes of non-relapse mortality after aHSCT.

T-cell immunoglobulin and mucin domain-containing 3 (TIM-3; also known as hepatitis A virus cellular receptor 2) is a negative regulator of T cells. TIM-3 was initially described as an inhibitory protein expressed on activated T helper (Th) 1 CD4+ and cytotoxic CD8+ T cells that secrete interferon-gamma (IFN-γ) (Monney et al 2002, Sánchez-Fueyo et al 2003). TIM-3 is enriched on FoxP3+ Tregs and constitutively expressed on DCs, monocytes/macrophages, and NK cells (Anderson et al 2007, Ndhlovu et al 2012). Further, TIM-3 has also been identified as an acute myeloid leukemia (AML) stem cell antigen that is present in leukemic blasts but not normal hematopoietic stem cells, and anti-TIM-3 antibody treatment has shown efficacy in blocking engraftment of AML in a mouse xenotransplantation model (Kikushige et al 2010). Promising preclinical and clinical anti-cancer activity has been reported for TIM-3 blockade (Kikushige et al 2010, Sakuishi et al 2010, Ngiow et al 2011, Sakuishi et al 2011, Jing et al 2015, Asayama et al 2017).

A sabatolimab-mediated enhancement of GvL could potentially exacerbate GvHD, an immune-mediated toxicity and the principal safety concern in the aHSCT setting. There are no reported data on the safety of sabatolimab in the post-aHSCT setting; therefore, an important safety objective is to assess the incidence and severity of treatment-emergent aGvHD and cGvHD, immune-related and other adverse events.

However, preliminary available data on sabatolimab indicate that associated irAEs appear to be limited and less frequent compared to PD-1 blockade.

This study will start with a Safety Run-in to assess whether sabatolimab can be administered in the post-aHSCT setting without unacceptable levels of treatment-emergent toxicities (dose limiting toxicities, ie; primary safety objective), including increased or worsening the risk of treatment emergent aGvHD or cGvHD, as well as severe immune-related toxicity during the first 2 cycles of study treatment.

The Safety Run-in will be conducted starting with a lower sabatolimab dose (400 mg IV Q4W) than what is currently being used in the MDS and AML setting outside of aHSCT setting (800 mg IV Q4W). If unacceptable toxicities are not observed, a new cohort of participants treated at 800 mg IV Q4W will subsequently be evaluated. Sabatolimab will then be evaluated at the recommended dose for expansion during Safety Run-in as monotherapy as well as in combination with azacitidine (See Section 4.3).

The preferred sabatolimab dose level for evaluation of efficacy in the study is 800 mg Q4W based on data accumulated from 2 phase 1 studies, [CMBG453X2101] and [CPDR001X2105] (Refer to Clinical Pharmacology, Clinical Efficacy, Clinical Safety, and Predicted Target Engagement below).

For further details, please refer to Section 1.1 and Section 1.2.

Clinical Pharmacology:

The pharmacokinetics (PK) of sabatolimab were similar between studies [CMBG453X2101] in solid tumor patients and [CPDR001X2105] in AML and high risk MDS patients. At lower doses (at 80 mg and below for Q2W dosing or at 240 mg and below for Q4W dosing), the PK was nonlinear, with faster elimination at lower concentrations. PK appeared linear with an approximate proportional dose-exposure (AUC and Cmax) relationship at doses of 240 mg and above for Q2W dosing and at doses of 800 mg and

above for Q4W dosing. Accumulation of sabatolimab was observed with repeated administrations, and for the Q2W regimen, AUCtau during cycle 3 ranged between 1.01-2.78 fold higher than during cycle 1. A dose of 800 mg Q4W has similar AUCtau as 400 mg Q2W at the steady state.

Clinical Efficacy:

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

Clinical Safety:

Sabatolimab was found to be safe and well tolerated across all dose levels tested in both studies. In study [CMBG453X2101], as of 25-Jul-2019, a total of 133 participants with solid tumors have been treated with sabatolimab single agent therapy. There were no adverse events attributed to study treatment with an incidence >10%. The most frequently reported adverse events attributed to study treatment included fatigue (9%), followed by decreased appetite and nausea (5% each). There were no DLTs during the first cycle. No participants discontinued study treatment due to treatment-related AEs.

In study [CPDR001X2105], as of 26-Jul-2019, a total of 123 participants with hematological malignancies have been treated with sabatolimab as a single agent (n=26) or in combination with decitabine (n=81) or azacitidine (n=16). In the 26 participants treated with sabatolimab single agent, there were no adverse events attributed to study treatment with an incidence >10%. The most frequently reported adverse event attributed to study treatment was a rash in two participants (8%). All other adverse events attributed to study treatment were single occurrences. There were no DLTs during the first cycle. No participants discontinued study treatment due to treatment-related AEs. In the 81 participants treated with sabatolimab in combination with decitabine, the most frequent adverse events (all grades, >10%) attributed to study treatment have included thrombocytopenia, anemia, neutropenia, nausea, and fatigue. One participant experienced a DLT during the first 2 cycles, which consisted of hepatitis manifesting as Grade 3 ALT increase. One participant discontinued study treatment due to a treatment-related adverse event (AE) of possible hemophagocytic lymphohistiocytosis. In the 16 participants treated with sabatolimab in combination with azacitidine, the most frequent adverse events (all grades, >10%) attributed to study treatment have included nausea, vomiting, anemia, constipation, neutrophil count decrease and platelet count decrease. There were no DLTs during the first 2 cycles. No participants discontinued study treatment due to treatment-related AEs. No study treatment-related deaths were observed in any of the studies mentioned above.

Preliminary analysis revealed no relationship between dose, incidence and severity of adverse events across the different treatment groups. No relationship was observed between Cmax and the incidence of potential immune related adverse events, providing additional support for 800 mg Q4W regimen, which has the highest Cmax among the doses tested. Please refer to the Investigator's Brochure for additional information of AEs reported in

participants with solid tumors or with hematologic malignancies treated with sabatolimab as a single agent or in combination with other drugs.

Predicted Target Engagement:

A population pharmacokinetic model of sabatolimab concentration was fit to all participants from [CPDR001X2105] and [CMBG453X2101] studies. This model was used to simulate the TIM-3 occupancy in the bone marrow by making assumptions about sabatolimab biodistribution to the bone marrow and binding affinity to TIM-3. Using trial simulation, this model predicted that the 800 mg Q4Wdose would give at least 95% receptor occupancy in at least 95% of participants at steady state Ctrough. This high degree of target engagement is also supported by a plateau in the accumulated soluble TIM-3 that is observed at doses of 240 mg Q2W and above, and at 800 mg Q4W and above.

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

Rationale for duration of treatment:

The proposed duration of treatment in this study is up to a maximum of 24 cycles, or until hematologic relapse, or unacceptable toxicity, whichever is earlier.

This is consistent with the RELAZA2 study where azacitidine was given for 24 cycles. After 6 cycles, participants with MRD negativity response (major response) were eligible for a treatment de-escalation (Platzbecker et al 2018).

This is also supported by the reported time to relapse post aHSCT in 1788 participants with AML with the majority of relapses occurring within the first 2 years post-aHSCT (median time to post-aHSCT relapse 7 months with 43% within <6 months and 39% between 6 months-2 years, and 18% beyond 2 years post-aHSCT) (Bejanyan et al 2015).

Although the optimal duration of therapy remains to be determined, the proposed 24 cycles would theoretically ensure maintenance of augmented GvL and suppression of residual leukemic cell growth for a prolonged period during the time post-aHSCT with the highest risk for relapse.

For participants who achieve and maintain MRD negativity for 12 consecutive cycles, study treatment may be discontinued earlier at investigator's discretion.

4.3 Rationale for choice and dose of combination drugs

After the completion of Safety Run-in and determination of the recommended dose for expansion, sabatolimab will be evaluated as monotherapy as well as in combination with azacitidine.

Azacitidine:

The dual activity of azacitidine as an antileukemic agent and inhibitor of GvHD makes it an attractive partner for combination with sabatolimab post-aHSCT to mitigate the potential risk of inducing or worsening of GvHD.

Azacitidine at 75 mg/m2 SC or IV x 7 days of every 28-day cycle in combination with sabatolimab at 800 mg IV Q4W has been evaluated in MDS and AML population and was found to be safe and tolerable (Borate et al 2020).

Azacitidine is currently not approved in the post aHSCT setting. However, azacitidine has been tested at different doses and schedules in various clinical studies in the post-aHSCT setting as preemptive or maintenance therapy of AML or MDS (see Section 1.1).

Based on the available published data on the safety and efficacy of various dosing regimens of azacitidine in the post-aHSCT setting (for further details, please see Section 1.1, azacitidine), lower doses of azacitidine were selected (50 mg/m2 SC x 5 days of every 28-day cycle) aiming to improve the tolerability of treatment with likely less hematological toxicities and infectious complications after aHSCT, enhance the adherence to treatment schedule and protocol compliance by reducing the burden of frequent hospital visits and increase the likelihood of a greater efficacy with the administration of more cycles of azacitidine (de Lima et al 2010**,** Goodyear et al 2012, Platzbecker et al 2012, Craddock et al 2016, Platzbecker et al 2018).

Of note, azacitidine dosing schedule of 50 mg/m2 SC x 5 days every 4 weeks has been studied in maintenance trials of AML after intensive chemotherapy (Griffin et al 2015, Huls et al 2019).

4.4 Rationale for MRD assessments [redacted]

4.4.1 Rationale for MRD assessments

Measurable Residual Disease (MRD) in AML refers to the presence of leukemic blasts at a sensitivity of detection below the threshold of conventional morphologic methods. participants who experience a CR according to morphologic assessments (<5% blasts in the bone marrow) can still harbor a large number of leukemic cells in the bone marrow, which confers poor outcome. Detection of MRD in AML has shown prognostic relevance in several studies (Freeman et al 2013, Terwijn et al 2013, Ivey et al 2016, Freeman et al 2018), indicating that the depth of leukemic clearance should be considered as a relevant prognostic endpoint in this setting.

The significance of MRD in hematopoietic stem cell transplantation is well recognized in AML. Indeed, there is a growing evidence that post-transplant MRD positivity is a prognostic biomarker of high-risk of relapse (Fang et al 2012, Appelbaum 2013, Zhou et al 2016, Shah et al 2018, Liu et al 2019, , Thol et al 2019). Furthermore, even pre-transplant MRD assessment by either MFC or molecular techniques can be used for risk stratification at the time of HSCT following either myeloablative or reduced intensity conditioning (Walter et al 2011, Buckley et al 2017, Canaani et al 2018, Gilleece et al 2018, Thol et al 2018).

To investigate in detail the depth of leukemic clearance, we will perform central MRD assessments using both phenotypic [redacted] methods. At present, Multiparameter Flow Cytometry (MFC) represents the most adequate, clinically validated technology to robustly monitor MRD in the large majority of AML participants (~90%), and recommended in the European Leukemia Net (ELN) 2018 MRD guidelines (Schuurhuis et al 2018b). For this reason, we plan to use MFC-MRD data as a secondary efficacy endpoint.

[redacted]

4.5 Purpose and timing of interim analyses/design adaptations

Interim analyses are planned for the monitoring of safety data (see Section 12.7).

The study design foresees that during and at the conclusion of Part 1 (Safety Run-in), decisions based on emerging data are made at safety review meetings following completion of enrollment at each dose level (or earlier if required) and prior to starting Part 2. The decision to escalate to the 800 mg Q4W dose level in Part 1 and the selection of the preferred

dose level for Part 2, will be based, principally, on the occurrence of dose limiting toxicities (DLTs) (see Table 6-2). The decision to open the combination cohort (cohort 3), the expansion monotherapy cohort (cohort 4) and the adolescent cohort (cohort 5) will be based on an overall assessment of all available data, including safety, preliminary response assessment, clinical pharmacology, tolerability, and recommendations from participating investigators. All the decisions will be guided by a Bayesian Logistic Regression Model (BLRM) to assess the relationship between the dose of MBG453 and the incidence of DLTs. If the probability that the true Dose Limiting Toxicity (DLT) rate exceeds 50% is less than 25%, the BLRM will recommend pursuing the recruitment and open a new cohort (see Section 6.5.2 for details on guidelines for determination of the recommended dose for expansion). These decisions will be communicated to investigators.

Details of this procedure and the process for communication with investigators are provided in Section 6.5.1 and Section 6.5.2.

The primary efficacy analysis will be performed after all participants of cohorts 3 and 4 have completed at least 6 cycles of study treatment or have been followed for at least 6 months after the first dose of study treatment or have discontinued from the study earlier. See Section 12.7.

Throughout the study, the decision whether or when to open an additional cohort(s) will be based on the overall safety, PK, tolerability, and preliminary response assessment.

4.6 Risks and benefits

The risk to participants in this trial will be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring. Further, dose modifications are recommended and must be applied per protocol based on clinical or laboratory findings (see Section 6.5.4).

Occurrence of an immune-related adverse event is an anticipated risk in participants treated with immune-oncology drugs such as sabatolimab. In the case of an immune-related event, there are dose modification and management guidelines, including detailed plans for follow-up of toxicities. In addition, the protocol references and requires adherence to the recent American Society of Clinical Oncology (ASCO) practices guidelines for the management of immune-related adverse events in patients treated with checkpoint inhibitors (Brahmer et al 2018) (see Section 6.5.5 and Section 6.5.5.2).

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

Furthermore, as the safety of sabatolimab monotherapy has not been assessed previously in the post- aHSCT setting, the protocol stipulates that consecutive safety run-in cohorts at 400 mg Q4W and 800 mg Q4W will be observed for at least 2 treatment cycles followed by a Safety Review Meeting, before opening enrollment to a larger participant population in Part 2 with a combination cohort (sabatolimab+ azacitidine) (Cohort 3), an expansion monotherapy cohort (Cohort 4) and an adolescent cohort (Cohort 5).

Sexually active males treated with azacitidine, and all women of child bearing potential enrolled in the study, must be informed that taking the study treatment may involve unknown risks to the fetus if a pregnancy were to occur during the study and must agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria . If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

SARS-CoV-2 and COVID-19 pandemic: No additional risk to participants' safety due to the SARS-CoV-2 virus and the COVID-19 pandemic has been identified with sabatolimab based on the available knowledge at this time, and therefore the benefit- risk remains unchanged. There is no contraindication for the use of an inactivated, viral-vector, or mRNA based SARS-CoV-2 vaccine in cancer patients on sabatolimab therapy.

COVID-19 vaccines have not been tested in patients treated with MBG453, therefore any additional risks are unknown. Before receiving any vaccine, the risks and benefits should be evaluated by the investigator. In case of active COVID-19 infection, a careful benefit- risk evaluation to be performed to determine whether participants can remain on study medication or not.

5 Study Population

The study population will include adult and adolescent participants with de novo AML or secondary AML, who have achieved complete remission (i.e., <5% bone marrow blasts, absence of circulating blasts in the blood, and absence of extramedullary disease) after aHSCT and at high risk of relapse defined by the presence of MRD (MRD+), any time at ≥ Day 60 after aHSCT.

Prior to enrollment, participants must have systemic GvHD prophylaxis or treatment [immunosuppressive treatment (IST)] completely tapered for at least two weeks prior to study entry, without any active grade III or IV acute GvHD, or moderate lung chronic GvHD, or any severe chronic GvHD. Prednisone dose ≤ 5 mg/day or equivalent corticosteroid dose is allowed.

A total of approximately 59 participants will be enrolled; including adults ≥ 18 years and a cohort of approximately 6 adolescent participants who are 12 years or older but less than 18 years old.

The exact number of participants enrolled will be determined by results obtained during the course of the study.

5.1 Inclusion criteria

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

1. Signed informed consent must be obtained prior to participation in the study.
2. At the date of signing the informed consent form (ICF), eligible participants must be ≥ 18 years for the adult cohorts; and ≥ 12 years old but < 18 years old for the adolescent cohort (cohort 5), which will open after completion of Safety Run-in.
3. Diagnosis of AML/secondary AML and received one prior aHSCT performed to control AML
   - Participants are eligible irrespective of response or MRD status at time of aHSCT
4. Participants in complete remission (< 5% bone marrow blasts, absence of circulating blasts, and absence of extramedullary disease) with MRD positivity by local assessment

or by central assessment where required (e.g., USA sites), any time at ≥ Day 60 after aHSCT.

5. Ability to provide a fresh bone marrow aspirate sample collected within 28 days from enrollment/randomization, and immediately shipped to a Novartis designated central laboratory for MRD testing.
6. Systemic GvHD prophylaxis or treatment [immunosuppressive treatment (IST)] completely tapered for at least two weeks prior to study entry. Prednisone dose ≤ 5 mg/day or equivalent corticosteroid dose is allowed.
7. Participants who are found with MRD positivity while still on or tapering systemic GvHD prophylaxis or treatment, MRD positivity must be re-confirmed at least 2 weeks after the last dose of IST
8. For the adult cohorts, participants must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2.

   For the adolescent cohort, participants must have a Karnofsky (age ≥ 16 years) or Lansky (age < 16 years) performance status score ≥ 50%.
9. AST and ALT ≤ 3 × upper limit of normal (ULN)
10. Total bilirubin ≤ 1.5 × ULN (except in the setting of isolated Gilbert syndrome, in which case higher total bilirubin is allowed provided that conjugated bilirubin is ≤ 1.5 x ULN)
11. Estimated Glomerular Filtration Rate (eGFR) ≥ 30 mL/min/1.73 m^2 (calculated, based on local laboratory, using the Modification of Diet in Renal Disease (MDRD) formula in adults, and using the bedside Schwartz formula in the adolescent cohort).
12. ANC ≥ $1.0x10^9$/L
13. Platelet count ≥ $75x10^9$/L
14. Written informed consent, willingness and ability to comply with all study procedures.
15. Haemoglobin level of ≥ 8 g/dL

5.2 Exclusion criteria

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

1. Prior exposure to TIM-3 directed therapy at any time.
2. History of severe hypersensitivity reactions to any ingredient of study drug(s) (azacitidine, sabatolimab) or monoclonal antibodies (mAbs) and/or their excipients
3. Human immunodeficiency virus (HIV) infection not controlled by standard therapy and/or with known history of opportunistic infection. For countries where HIV status is mandatory: HIV status will be tested during screening using a local test.
4. Active Hepatitis B (HBV) or Hepatitis C (HCV) infection. Participants whose disease is controlled under antiviral therapy should not be excluded.
5. Active acute GvHD grade III-IV according to standard criteria (Appendix 1).
6. Active moderate chronic GvHD of the lungs according to NIH consensus criteria (Appendix 2).

   Active severe chronic GvHD according to NIH consensus criteria.
7. Psychiatric disorder that interferes with ability to understand the study and give informed consent or patient information assent for adolescent, and/or impacts study participation or follow-up.

8. History of another primary malignancy that is currently clinically significant or currently requires active intervention. Participants who are receiving adjuvant therapy, such as hormone therapy, are eligible.
9. Any concurrent severe and/or active uncontrolled infection requiring parenteral antibacterial, antiviral or antifungal therapy (such as severe pneumonia, meningitis, or septicemia)
10. Other concurrent severe and/or uncontrolled medical conditions (e.g. uncontrolled diabetes mellitus, chronic obstructive or chronic restrictive pulmonary disease including dyspnoea at rest from any cause) or history of serious organ dysfunction or disease involving the heart, kidney, or liver.
11. Other co-morbidity that, in the opinion of the investigator, predisposes the participant to high risk of noncompliance with the protocol.
12. Active autoimmune disease requiring systemic therapy (e.g. corticosteroids). Topical, inhaled, nasal and ophthalmic steroids are not prohibited. Replacement corticosteroids therapy is allowed and not considered a form of systemic treatment
13. Live vaccine administered within 30 days prior to the first day of study treatment (C1D1)
14. Cardiac or cardiac repolarization abnormality, including but not limited to any of the following:

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

    b) Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third-degree AV block)
15. Female is pregnant or breastfeeding. Negative serum pregnancy test is required for women of child-bearing potential (WOCBP).
16. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during study treatment and for 90 days after the last dose of azacitidine (or as per the respective local label, whichever is longer) and 150 days after the last dose of sabatolimab. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening/baseline). For female participants on the study the vasectomized male partner should be the sole partner
    - Use of oral (estrogen and progesterone), injected or implanted combined hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

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

Women of non-childbearing potential, defined as women who are physiologically and/or anatomically incapable of becoming pregnant, as now further described:

- They are post-menopausal as evidenced by 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e., age-appropriate history of vasomotor symptoms), or,
- they have had bilateral surgical oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least 6 weeks prior to first dose. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment, is she considered not of childbearing potential.

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

17. Sexually active males unless they use a condom during intercourse while taking azacitidine and for 3 months after stopping this drug. They should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. In addition, male participants must not donate sperm for the time period specified above.
18. Prior systemic AML/cancer-directed treatments given at any time after aHSCT; or investigational modalities ≤ 5 half-lives or 4 weeks prior to starting study, whichever is shorter. Prior prophylactic use of DLI with or without hypomethylating agent (HMA) is permitted, if DLI is completed ≥ 3 months, and HMA is completed ≥ 4 weeks prior to start of study treatment.
19. Participants with BCR-ABL mutant AML who are eligible for post-transplant tyrosine kinase inhibitor therapy as per investigator clinical assessment and local practice guidelines

6 Treatment

6.1 Study treatment

In this study, the term “investigational drug” refers to the Novartis study drug, sabatolimab (MBG453).

The term “study treatment” refers to the combination of study drugs: sabatolimab plus azacitidine or sabatolimab alone.

All doses prescribed, dispensed to the participant and all dose changes during the study including the reason must be recorded on the appropriate electronic case report form (eCRF) page.

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Dose for Administration	Frequency /Regimen	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
Sabatolimab 400 mg/4ml	400 mg 800 mg	Q4W	Solution in vial for IV infusion	Intravenous use	Open label	Sponsor (global)
Azacitidine* 100 mg as per local /global supply	50 mg/m^2	Days 1-5 of each cycle	Vial for IV infusion or subcutaneous administration$	Intravenous or subcutaneous administration$	Open label	Sponsor (global) or provided locally

* Azacitidine will be used only in the Combination cohort.
$ Intravenous or subcutaneous azacitidine should not be substituted by oral azacitidine (CC-486, Onureg®). The indications and dosing regimen for intravenous or subcutaneous azacitidine differ from that of oral azacitidine (CC-486, Onureg®).

Sabatolimab

Sabatolimab will be administered at an assigned dose level, 400 mg or 800 mg, via IV infusion over 30 minutes (up to 2 hours, if clinically indicated) on Day 1 of each 28-day treatment cycle for participants in the sabatolimab monotherapy cohorts; and on Day 5 (+/- 3 days except for Cycle 1 where sabatolimab should not be administered earlier than Day 5, after the participant has received at least 5 doses of azacitidine) of each 28-day treatment cycle in the combination cohort. There should be a period of at least 1 hour after the infusion whereby the participant requires close observation.

On days of co-administration of azacitidine and sabatolimab (e.g. on Day 5 of a cycle), the azacitidine should be administered first followed by sabatolimab. A minimum of one hour break between azacitidine administration (IV or SC) must be applied before starting the sabatolimab infusion.

Further instructions for the preparation and dispensation of sabatolimab is described in the Pharmacy Manual.

Azacitidine (Combination Cohort 3 only)

Azacitidine will be administered at a dose of 50 mg/m^2; body surface area (BSA) in m^2 = [height (cm) x weight (kg)/3600]$^{0.5}$), SC or IV every day for five consecutive days on Days 1-5 out of a 28 days cycle (for further details except the dose and schedule, see local azacitidine prescribing information or (Vidaza (Azacitadine) USPI 2008).

The azacitidine regimen used in this protocol was selected based on the available data from various clinical studies testing azacitidine at different doses and schedules in the post-aHSCT setting as preemptive or maintenance therapy of AML or MDS (de Lima et al 2010, Goodyear et al 2012, Platzbecker et al 2012, Craddock et al 2016, Platzbecker et al 2018). Please refer to Section 1.1, Section 1.2 and Section 4.3 for background, purpose and rationale. Lower doses of azacitidine (50 mg/m^2 SC x 5 days of every 28-day cycle)

were selected in attempt to improve tolerability of treatment with likely less hematological toxicities and infectious complications after aHSCT; and to enhance adherence to schedule and protocol compliance by reducing the burden of frequent hospital visits.

Intravenous or subcutaneous azacitidine should not be substituted by oral azacitidine (CC-486, Onureg®). The indications and dosing regimen for intravenous or subcutaneous azacitidine differ from that of oral azacitidine (CC-486, Onureg®).

6.1.2 Additional study treatments

No other study treatment beyond investigational drugs (sabatolimab and azacitidine) is included in this trial.

6.1.3 Treatment arms/group

In Part 1 (Safety Run-in), participants enrolled in cohort 1 will receive sabatolimab 400 mg Q4W, and participants enrolled in cohort 2 will receive sabatolimab 800 mg Q4W.

Participants enrolled in Part 2 will receive sabatolimab in monotherapy at the recommended dose for expansion determined in the Safety Run-in (either 400 mg Q4W or 800 mg Q4W) in cohorts 4 and 5 (monotherapy expansion cohort and adolescent cohort respectively), or sabatolimab in combination with azacitidine in cohort 3 (combination cohort).

6.1.4 Guidelines for continuation of treatment

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

6.1.5 Treatment duration

Study treatment will be administered for up to a maximum of 24 cycles or until a participant experiences hematologic relapse (bone marrow blasts ≥5%; or reappearance of blasts in the blood; or development of extramedullary disease) as defined by ELN 2017 (Döhner et al 2017); or any of the following events, whichever is earlier:

- unacceptable toxicity
- initiation of a treatment cycle is delayed due to toxicities by more than 28 days (measured from the intended start date of the new cycle (i.e. measured from Day 29 of the previous cycle)
- withdrawal of consent
- physician decision
- lost to follow up
- pregnancy
- death

For participants who achieve negative MRD and maintain MRD negativity for 12 consecutive cycles, study treatment (sabatolimab monotherapy or sabatolimab in combination with azacitidine) can be discontinued earlier, at the discretion of the PI.

6.1.5.1 Treatment beyond disease progression

Treatment beyond hematologic relapse is not permitted.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

In general, the use of any concomitant medication/therapy deemed necessary for the care of the participant (e.g., such as anti-emetics, anti-diarrheal) is permitted (see Section 6.2.1.1), except when specifically prohibited (see Section 6.2.2). The participant must be told to notify the investigational site about any new medications he/she takes after the start of the study drug.

Participants should not receive pre-medication to prevent infusion reaction before the first infusion of sabatolimab. If a participant experiences an infusion reaction, he/she may receive pre-medication on subsequent dosing days. The pre-medication should be chosen per institutional standard of care, at the discretion of the treating physician. If a participant experiences a Grade 3 infusion reaction (which does not resolve within 72 hrs) or Grade 4 infusion reaction, the investigational drug (sabatolimab) should be discontinued (see Table 6-3).

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

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

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

For participants enrolled all medications, procedures, and significant non-drug therapies/procedures (including physical therapy) taken within the 28 days of screening until 150 days after the last dose of sabatolimab or 30 days after the last dose of azacitidine administered, whichever is later, or until start of a new antineoplastic therapy must be recorded in the appropriate Case Report Forms. Concomitant medication administered to treat AE/SAEs suspected to be related to study treatment will continue to be collected up to the end of the safety follow-up period.

The approved drug labels for azacitidine should be consulted for guidance on concomitant therapies.

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

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Anticoagulation therapy is permitted if the participants are already at stable dose of warfarin or stable doses of low molecular weight heparin (LMWH) for > 2 weeks at time of first dose and International Normalized Ratio (INR) should be monitored as clinically indicated per investigator's discretion. Participants who develop a new requirement for anticoagulant

therapy during the conduct of the study may remain on study after documented discussion with the Novartis medical monitor. However, ongoing anticoagulant therapy should be temporarily discontinued to allow bone marrow sampling according to the institutional guidelines.

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

6.2.2 Prohibited medication

During the course of study treatment, participants must not receive additional investigational drugs or devices, chemotherapy, DLI, other cellular therapies or any other therapies that may be active against cancer or modulate the immune response. Post treatment efficacy follow-up period will end, once a participant develops a hematologic relapse, or start of new therapy for AML.

Additionally, the use of systemic corticosteroids and/or immunosuppressive medications is not allowed while on study treatment unless given for the management of infusion-related reaction, treatment-emergent immune-related adverse events (irAEs), aGvHD and/or cGvHD.

Systemic corticosteroids required for control of infusion-related reactions or irAEs must be tapered and be at non-immunosuppressive doses (≤ 10 mg/day of prednisone or equivalent corticosteroid dose) before the next study administration. If more than 10 mg/day prednisone is used, sabatolimab should be interrupted until the participant receives 10 mg/day or less of prednisone. Topical, inhaled, non-absorbable, nasal and ophthalmic steroids are allowed.

For aGvHD and/or cGvHD, refer to Table 6-4.

The use of systemic steroids and/or other immunosuppressive drugs may be administered for prophylaxis against imaging contrast dye allergy (providing this is ≤ 10 mg/day prednisone or equivalent corticosteroid dose), or replacement-dose steroids in the setting of adrenal insufficiency, or for the management of transient exacerbation of other underlying diseases such as chronic obstructive pulmonary disease requiring treatment for ≤ 3 weeks.

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

In addition, prohibited medication related to azacitidine will apply according to local/global label.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for prescreening (if applicable) or screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each

participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

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

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

6.3.2 Treatment assignment, randomization

This phase Ib/II trial is an open label study.

- In the Part 1 (safety run-in part), the study is non-randomized, and participants will be treated with sabatolimab in monotherapy
- In the Part 2, adult participants will be randomized to one of the two cohorts: combination cohort (Cohort 3 with sabatolimab + azacitidine as study treatment) and expansion monotherapy cohort (Cohort 4 with sabatolimab monotherapy as study treatment). The randomization ratio will depend on the number of participants from the safety-run in part (Part 1) already treated with sabatolimab at the selected dose level for expansion. If the sabatolimab dose selected for expansion is the 800 mg dose level and if 12 participants are included in the safety run-in part at that dose level, participants will be randomized in a 1:1.5 ratio to one of the two adult cohorts in Part 2. Thus, 25 participants will be treated with sabatolimab in monotherapy at the selected dose level (12 participants from the safety run-in cohorts and 13 participants from the expansion monotherapy cohort) and 20 participants will be treated with sabatolimab at the selected dose given in combination with azacitidine (20 participants from the combination cohort).
- In Part 2, adolescent participants will be enrolled in Cohort 5 with sabatolimab monotherapy.

For the randomization part (Cohort 3 and Cohort 4):

Following completion of screening procedures and prior to receive the first dose of study treatment, all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the two cohorts: Cohort 3 with the combination sabatolimab + azacitidine or Cohort 4 with sabatolimab in monotherapy. The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment and will specify a unique medication number for the first package of sabatolimab to be dispensed to the participant. Study treatment azacitidine will be supplied by Sponsor (global) or sourced locally for participants randomized in Cohort 3.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

The randomization scheme for participants will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment blinding

Treatment will be open to participants, investigator staff, persons performing the assessments, and the CTT.

6.5 Dose escalation and dose modification

Two dose levels of sabatolimab, 400mg Q4W and 800mg Q4W will be evaluated. Intra-participant dose escalation is not permitted at any time during the study. Guidance for dose modifications is provided in Section 6.5.

6.5.1 Dose escalation guidelines

Sabatolimab will be given at 400 mg IV every 4 weeks in the first cohort including approximately 8 participants (to obtain at least 6 evaluable participants). If there is no unacceptable level of toxicity during the first 2 cycles at this dose level, sabatolimab will be given at 800 mg IV every 4 weeks in the second cohort including approximately 12 participants (to obtain at least 9 evaluable participants).

The level of toxicity will be assessed by the number of dose-limiting toxicities as defined in Table 6-2.

Guidelines for dose escalation and for determination of the recommended dose for expansion are presented in Section 6.5.2.

In case of safety concerns and/or based on pharmacokinetic/pharmacodynamic data during the safety run-in part of the study (Part 1), the following changes may be considered:

- To include additional participants at the current dose level
- To not escalate to the next planned dose (sabatolimab 800 mg Q4W)

6.5.2 Guidelines for determination of the recommended dose for expansion (RDE)

The recommended dose for expansion (RDE) of sabatolimab will be the highest dose level between 400 mg and 800 mg Q4W that is not expected to cause an unacceptable level of toxicity (DLT) including aGvHD and cGvHD in more than 50% of the treated participants during the DLT evaluation period (See Table 6-2).

Notably, the curative efficacy of aHSCT is attributable to GvL, which inherently maybe associated with risk of GvHD, with reported incidence rates of clinically significant aGvHD ranging from 9% to 50%, and cGvHD from 30% to 70% (see Section 1.1). Therefore, post-

aHSCT immunomodulatory interventions, including sabatolimab, that promote GvL could potentially induce GvHD and other immune-related adverse events.

However, the assessment of whether GvHD or unacceptable level of toxicity is possibly treatment-related, and therefore a DLT, will be confounded by the inherent background incidence of GvHD associated with aHSCT. As the reported incidence of acute and chronic GvHD is similar to or in some cases higher than the standard threshold for incidence of DLT in phase I studies (i.e. DLT rate < 33.3%), a higher threshold (DLT rate of 50%) was selected for the Bayesian model to determine if sabatolimab given as monotherapy is not meeting an unacceptable level of toxicity.

However, all toxicities ≥ grade 2 will be individually reviewed to evaluate safety data of each cohort from the Safety Run-in part.

In the first cohort, approximately 8 participants (to obtain at least 6 evaluable participants) will be treated with the starting dose of sabatolimab 400 mg every 4 weeks.

In the second cohort, approximately 12 participants (to obtain at least 9 evaluable participants) will be treated with sabatolimab 800 mg every 4 weeks.

For both cohorts, participants must complete a minimum of 2 cycles of treatment with the minimum safety evaluation and drug exposure or have had at least one dose-limiting toxicity (DLT) including aGvHD and cGvHD within the first 2 cycles of treatment to be considered evaluable for dose escalation/expansion decisions. Dose escalation/expansion decisions will occur when the cohort of participants have met these criteria.

Dose escalation/expansion decisions will be made by Investigators and Novartis study personnel (including the study physician and statistician) during a dose decision meeting by teleconference. Decisions will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study including safety information, incidence and severity of aGvHD and cGvHD, incidence of DLTs, all Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 2 toxicity data during the first two cycles, available PK and PD data from evaluable participants.

The recommended dose for the next cohort of participants (second cohort in the safety run-in part, expansion cohort, combination cohort and adolescent cohort) will be guided by a Bayesian logistic regression model (BLRM) and by applying the following principle: the risk to have ≥ 50% DLTs including GvHD must be below 25%. This adaptive Bayesian methodology has the advantage to incorporate information gained at the preceding dose levels. Thus, additional participants may be enrolled at this dose level or a higher dose level as agreed by Investigators and Novartis personnel and if the BLRM predicts that the risk to have ≥ 50% dose limiting toxicities (DLTs) including GvHD remains below 25%.

Sabatolimab administration at the next higher dose level (sabatolimab 800 mg Q4W) or starting the recruitment of the Part 2 of the study (monotherapy expansion cohort, combination cohort and adolescent cohort) may not proceed until the investigator receives written confirmation from Novartis indicating that the results of the previous cohort were evaluated and that it is permissible to proceed to open a new cohort.

6.5.3 Definitions of dose limiting toxicities (DLTs)

Dose-limiting toxicities will be collected and evaluated in participants enrolled to the Safety Run-in part and adolescent cohort.

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value considered by the Investigator to be at least possibly related to sabatolimab as a single contributor that occurs during the DLT observation period [during the first 2 cycles, ie, Cycle 1 Day 1 (starting from the first infusion of sabatolimab) to the end of Cycle 2 of treatment with sabatolimab monotherapy in Safety Run-in] and meets any of the criteria included in Table 6-2. The National Cancer Institute Common Terminology Criteria for Adverse events (NCI CTCAE) version 5.0 will be used for all grading, except for GvHD (Harris et al 2016 for aGvHD and NIH consensus criteria for cGvHD). For the purpose of dose-escalation decisions, DLTs will be considered and included in the BLRM.

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

For aGvHD and/or cGvHD that meet DLT criteria, refer to Table 6-4 for study treatment interruption, re-initiation and/or discontinuation.

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

Table 6-2 Criteria for Dose Limiting Toxicities (DLTs)

Toxicity	DLT Criteria
DLTs considered related to graft vs host disease (GvHD) by the Investigator assessment	
Acute GvHD	Grade IV acute GvHD
	Stage ≥3 lower GI acute GvHD (consistent with Grade III acute GvHD)
	Stage ≥3 liver acute GvHD (consistent with Grade III GvHD)
Chronic GvHD	Moderate chronic GvHD of the lungs
	Severe chronic GvHD
Other DLTs excluding acute or chronic GvHD by the investigator assessment	
Immune-related adverse events (irAEs)	- irAEs ≥ CTCAE Grade 3 persisting > 7 days after starting appropriate treatment (e.g. with corticosteroids) - Pneumonitis ≥ CTCAE Grade 2 persisting > 7 days despite treatment with corticosteroids - Pneumonitis ≥ CTCAE Grade 3
Hematology	- Febrile neutropenia ≥ CTCAE Grade 3 in the absence of leukemic involvement in the marrow - Thrombocytopenia ≥ CTCAE Grade 3 with clinically significant bleeding in the absence of leukemic involvement in the marrow - Grade 4 neutropenia, thrombocytopenia, and pancytopenia, not related to leukemic infiltration, and do not respond to growth factor or transfusion support within 14 days will be considered to be a DLT (BM evaluation may be required to determine if marrow aplasia is due to leukemia).
Infusion related reactions	Infusion reaction CTCAE Grade 3 that does not resolve to Grade 1 within 72 hours or CTCAE grade 4 of any duration.

Toxicity	DLT Criteria
Other	Any other unacceptable non-hematological toxicity encountered by a participant as determined by the Investigators and Novartis.

6.5.4 Dose modifications

For participants who do not tolerate the protocol-specified dosing schedule, dose interruptions are required to allow participants to continue the study treatment.

Dose modifications for sabatolimab

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

Additionally, the guidance indicated in Table 6-3 below, provides instructions for infusion reaction, immune-related adverse events not covered by ASCO guidelines and a general guideline for non-hematologic non-immune-related toxicities that are clinically significant per investigator judgement and possibly attributable to the investigational drug. This general guideline will not apply in case of non-hematologic non-immune-related toxicities that are attributable to azacitidine and its complications.

Deviations to dose interruptions, reductions and/or permanent discontinuations outlined in Table 6-3 are not allowed.

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

Overall, for adverse events of potential immune-related etiology (other than GvHD) that do not recover to ≤ Grade 1 or baseline and be maintained at a dose of immunosuppression of ≤ 10 mg/day prednisone or equivalent (or as indicated in Table 6-3 within 12 weeks after initiation of immunosuppressive therapy), sabatolimab must be permanently discontinued.

For acute and/or chronic GvHD, refer to Table 6-4 for study treatment interruption, re-initiation and/or permanent discontinuation.

Dose interruption at the start of a new treatment cycle (Combination cohort)

In participants who have Grade 4 neutropenia and/or Grade 4 thrombocytopenia dosing of azacitidine should be interrupted until resolution to ≤ Grade 2. Sabatolimab should not be administered during azacitidine dose interruption. After resolution, dosing of azacitidine may be resumed on the same day. The first day dosing is resumed will be considered as D1 of the new treatment cycle and sabatolimab will be administered on Day 5 of the new cycle. In participants who achieved CRi or MLFS, azacitidine has been permanently discontinued, remain on sabatolimab, but have Grade 4 neutropenia and/or Grade 4 thrombocytopenia; dosing of sabatolimab should be interrupted until resolution to ≤ Grade 2. The first day dosing with sabatolimab is resumed will be considered D5 of the new cycle.

For study treatment interruption for acute and/or chronic GvHD, refer to Table 6-4.

Table 6-3 Criteria for dose interruption, re-initiation and discontinuation of sabatolimab due to adverse drugs reactions

Worst Toxicity Grade (CTCAE v5.0)	Recommended Dose Modifications
Infusion Reaction	
Grade 1	Decrease infusion rate until recovery
Grade 2	Stop infusion Before restarting – pre-medicate according to local institutional guidelines. Restart infusion at 50% of previous rate under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion(s)If the AE recurs at the reinitiated slow rate of infusion, and despite oral pre-medication*, then discontinue MBG453
Grade 3	Stop infusion If the AE resolves to ≤ Grade 1 within 72hrs: · At next scheduled treatment visit, pre-medicate according to local institutional guidelines. · Restart infusion at 50% of previous rate under continuous observation. Ensure that there is a minimum observation period of 1 hour · If the AE recurs despite slow rate of infusion and pre-medication*, then discontinue sabatolimab If the AE does not resolve to ≤ Grade 1 within 72hrs: · Discontinue sabatolimab
Grade 4	Discontinue sabatolimab
For adverse events thought to be immune-related and not covered in the ASCO Guidelines for the management of immune-related adverse events in participants treated with immune checkpoint inhibitor therapy (Brahmer et al 2018**)**	
Grade 1	Continue treatment with sabatolimab
Grade 2 or Grade 3 ≤ 7 days	Delay treatment with sabatolimab until resolved to ≤ Grade 1 or baseline
Grade 3 lasting > 7 days but < 21 days	1st and 2nd occurrence: Delay study treatment until resolved to ≤ Grade 1 or baseline 3rd occurrence: Discontinue study treatment
Grade 3 lasting ≥ 21 days Or Grade 4	Discontinue study treatment
Dermatological toxicities	
Grade 1	Maintain sabatolimab. Use topical steroids, antihistamines, topical emollients.
Grade 2	Consider interrupting sabatolimab. Use topical or oral steroids, antihistamines. If sabatolimab is interrupted and resolution to ≤ Grade 1, restart sabatolimab.
Grade 3 or 4	Interrupt sabatolimab. Manage per institutional practice. After resolution to ≤ Grade 1, consider restarting sabatolimab.
Bullous dermatitis	Grade 1, 2, and 3: Interrupt sabatolimab. Consult with dermatologist for appropriateness to restart sabatolimab.

Worst Toxicity Grade (CTCAE v5.0)	Recommended Dose Modifications
	Grade 4: Permanently discontinue sabatolimab.
Stevens-Johnson syndrome (SJS) or Lyell syndrome/toxic epidermal necrolysis (TEN)	Permanently discontinue sabatolimab.
For non-hematological, non-immune related adverse events clinically significant and possible attributable to the investigational drug (NCI CTCAE v5.0)** (The guideline does not apply to for toxicities attributable to azacitidine or the underlying AML including its complications)	
Grade 1 and Grade 2 tolerable	Continue treatment with sabatolimab
Grade 2 intolerable and Grade 3	1st or 2nd occurrence: · Interrupt sabatolimab until toxicity recovers to ≤ Grade 1 or baseline · Once recovered to ≤ Grade 1 or baseline restart sabatolimab at the same dose level and schedule AE resolution to ≤ Grade 1 or baseline must occur within a maximum period of 56 days since interruption, otherwise sabatolimab must be permanently discontinued. 3rd occurrence: · Permanently discontinue sabatolimab
Grade 4	Discontinue sabatolimab

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

Dose modifications for azacitidine (Combination cohort)

If azacitidine is deemed by the investigator to possibly have contributed to an observed adverse event, the dose or schedule of azacitidine may be modified within a cycle and/or for subsequent cycles, or temporarily interrupted, or permanently discontinued.

Permanent discontinuation of sabatolimab and azacitidine (Combination cohort)

If the study treatment (sabatolimab + azacitidine) is interrupted for toxicities other than GvHD and the start of the subsequent study treatment cycle is delayed for more than 28 consecutive days from the intended start date of cycle (Day 29 of the previous cycle) the participant should be discontinued from study treatment. For permanent discontinuation of study treatment due to acute and/or chronic GvHD, refer to Table 6-4.

Permanent discontinuation of only one component sabatolimab (or azacitidine - Combination cohort)

If **one component only** of the study treatment (azacitidine or sabatolimab) is discontinued for toxicities (other than GvHD), then the treatment may continue with the other component of study treatment alone (sabatolimab alone or azacitidine alone) as long as the participant benefits per investigator's judgement.

These dose changes must be recorded on the appropriate CRF.

Table 6-4 Criteria for dose interruption, re-initiation and discontinuation of study treatment due to GvHD

	Interrupt study treatment[£] (sabatolimab monotherapy or in combination with azacitidine)	**Resume study treatment (sabatolimab monotherapy or in combination with azacitidine)**	**Discontinue study treatment permanently** (sabatolimab monotherapy or in combination with azacitidine)

Acute GvHD (aGvHD)	• New onset grade II requiring systemic therapy
	• New onset grade III
	• Baseline grade I or II worsening to grade III
		• If aGvHD improved to ≤ grade I or to baseline prior to starting study treatment within ≤ 8 weeks of observation from onset or exacerbation of aGvHD
		• The following are allowed at time of resumption of study treatment:
		  • Topical, non-absorbable or inhaled steroids
		  • Systemic doses of steroids ≤ 10 mg prednisone or equivalent
		  • Tacrolimus with trough levels <5 ng/mL OR CSA with trough levels <200 ng/mL (indicating continuous IST taper)
			• Grade IV aGvHD
			• Recurrence or exacerbation of aGvHD to ≥ grade III after resuming study treatment
			• Steroid-refractory aGvHD
			• No improvement to ≤ grade I or to baseline prior to starting study treatment after 8 weeks of observation from onset or exacerbation of aGvHD

Chronic GvHD (cGvHD)	• New onset moderate cGvHD ONLY if requires systemic therapy with > 5 mg prednisone or equivalent	• If cGvHD improved to ≤ mild cGvHD or to baseline prior to starting study treatment within ≤ 8 weeks of observation from onset or exacerbation of aGvHD	• Severe cGvHD • Moderate cGvHD of the lungs • Baseline moderate cGvHD worsening to severe cGvHD • Recurrence or exacerbation of cGvHD to

	Interrupt study treatment[£] (sabatolimab monotherapy or in combination with azacitidine)	**Resume study treatment (sabatolimab monotherapy or in combination with azacitidine)**	**Discontinue study treatment permanently** (sabatolimab monotherapy or in combination with azacitidine)

		• The followings are allowed at time of resumption of study treatment:
		  • Topical, non-absorbable or inhaled steroids
		  • Systemic doses of steroids ≤ 10 mg prednisone or equivalent
		  • Tacrolimus with trough levels <5 ng/mL OR CSA with trough levels <200 ng/mL (indicating continuous IST taper)
			moderate cGvHD that requires systemic therapy with > 5 mg prednisone or equivalent; severe cGvHD; or moderate cGvHD of the lung after resuming study treatment
			• Steroid refractory cGvHD
			• No improvement to ≤ mild or to baseline prior to starting study treatment after 8 weeks of observation from onset or exacerbation of cGvHD

[£]Treatment of GvHD at the discretion of the treating investigator

6.5.5 Follow-up for toxicities

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

All participants in Safety Run-in, expansion monotherapy, and adolescent cohorts must be followed up for AEs (including but not limited to acute and chronic GvHD, irAEs and SAEs) for 150 days following the last dose of sabatolimab.

All participants in combination cohort must be followed up for AEs (including but not limited to acute and chronic GvHD, irAEs and SAEs) for 30 days following the last dose of azacitidine and 150 days following the last dose of sabatolimab, whichever is later.

In addition to the instructions provided in this section, please refer to Section 16.3 (Appendix 3) for further guidance on renal alert criteria, actions and events follow up.

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

Guidelines for follow-up on potential DILI cases are described in Table 6-5 and Table 6-6.

Table 6-5 Follow-up of abnormal liver chemistry results

ALT	TBL	Liver Symptoms	Action
ALT increase without bilirubin increase:			
If normal at baseline: ALT > 3 x ULN If elevated at baseline: ALT > 2 x baseline or > 200 U/L (whichever occurs first)	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	- No change to study treatment - Measure alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), TBIL, INR, albumin, lactate dehydrogenase (LDH), CK, and glutamate dehydrogenase (GLDH) in 48-72 hours. - Follow-up for symptoms
If normal at baseline: ALT > 5 x ULN for more than two weeks If elevated at baseline: ALT > 3 x baseline or > 300 U/L (whichever occurs first) for more than two weeks	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	- Interrupt study drug - Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, LDH, CK, and GLDH in 48-72 hours. - Follow-up for symptoms. - Initiate close monitoring and workup for competing etiologies. - Study drug can be restarted only if another etiology is identified, and liver enzymes return to baseline.
If normal at baseline: ALT > 8 x ULN	Normal	None	
ALT increase with bilirubin increase:			
If normal at baseline: ALT > 3 x ULN If elevated at baseline: ALT > 2 x baseline or > 200 U/L (whichever occurs first)	TBL > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
If normal at baseline: ALT > 3 x ULN If elevated at baseline: ALT > 2 x baseline or > 200 U/L (whichever occurs first)	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	

Table 6-6 Action required for isolated total bilirubin elevation

Abnormality	Action required
Any elevation > ULN	Fractionate bilirubin, evaluate for cholestatic liver injury (ALP) or alternative causes of bilirubin elevation. Treat alternative causes according to local institutional guidelines
Grade 2 (>1.5 - 3.0 ULN)	Maintain treatment. Repeat LFTs within 48-72 hours, then monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline
Grade 3 (>3.0 – 10 ULN)	Interrupt treatment. Repeat LFTs within 48-72 hours, then monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline
Grade 4 (> 10 x ULN)	Discontinue study treatment

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

1. A detailed assessment of potential treatment emergent GvHD of liver (acute or chronic) should be performed by the Investigator
2. A detailed history, including relevant information, such as cardiac disease, history of any pre-existing liver conditions or risk factors, blood transfusions, IV drug abuse, travel, work, alcohol intake, and full clinical examination for evidence of acute or chronic liver disease, cardiac disease and infection etc. should be performed.
3. Review of concomitant medications, including nonprescription medications and herbal and dietary supplement preparations, alcohol use, recreational drug use, special diets, and chemicals exposed to within one month of the onset of the liver injury.
4. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
5. Obtain an unscheduled PK sample, as close as possible to last dose of study treatment.

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

6.5.5.2 Follow-up for immune -related AEs

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

An irAE is any clinically significant AE affecting any organ that is associated with study drug exposure, is consistent with an immune-mediated mechanism, and where alternative explanations have been investigated and ruled out or are considered to be unlikely. Serologic, histologic and immunological assessments should be performed as deemed appropriate by the Investigator, to verify the immune related nature of the AE. An empiric trial of corticosteroids may also contribute to understanding the etiology of a potential irAE.

However, in the post-aHSCT setting, acute and chronic GvHD manifestations may overlap and be challenging to distinguish from irAEs [eg, skin rash, liver (hyperbilirubinemia, cholestasis, transaminitis), diarrhea, pneumonitis, etc.].

All participants with signs or symptoms of irAEs not attributed to acute or chronic GvHD should be monitored and managed following the ASCO Guidelines for the management of immune-related adverse events in participants treated with immune checkpoint inhibitor therapy (Brahmer et al 2018). For irAEs not covered by ASCO guidelines, please refer to Table 6-3.

In case of a suspected irAE not attributed to acute or chronic GvHD, the relevant immunological assessments (e.g. rheumatoid factor, anti-DNA Ab, etc.) should be performed. In case of a toxicity suspected to be a cytokine release syndrome, the cytokine assessments outlined in Table 8-9 must be performed.

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

6.5.5.3 Follow-up for QTcF Prolongation

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

- Assess the quality of the ECG recording. Collect two additional ECGs as soon as possible.
- Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia, hypocalcemia). If abnormal, correct abnormalities.
- Review concomitant medication use for possible causes for QT prolongation (refer to crediblemedicines.org). Record all concomitant medications in the appropriate eCRF page.
- Monitor ECG per the institutional standards.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Every time the investigational treatment sabatolimab is to be administered, IRT must be accessed to assign a medication (kit) number to the participants. The date and time of all study treatment administration sabatolimab during the study and any deviations from the protocol treatment schedule will be captured by the investigator staff and reviewed by field monitor on the appropriate study treatment dispensing form. Compliance with the study treatment will be assessed by the field monitor at each visit and information provided by the pharmacist or by the investigator. All study treatment dispensed, returned or destroyed as per local regulation must be recorded in the Drug Accountability Log.

Pharmacokinetic parameters will be determined in all participants as detailed in the pharmacokinetics Section 8.5.2.

All dosages for sabatolimab as well as azacitidine (Combination cohort) prescribed to the participant and all dose changes during the study must be recorded on the corresponding Dosage Administration Record.

6.7 Preparation and dispensation

The investigator or responsible site personnel must instruct the participant or caregiver to take the study treatment as per protocol. Study drug(s) will be dispensed to the participant by authorized site personnel only. A unique medication number is printed on the study medication label. All dosages for study treatment sabatolimab prescribed to the participant and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

Sabatolimab

Each study site will be supplied by Novartis with the investigational drug sabatolimab as global clinical open supply and will be packed and labelled under the responsibility of Novartis. Investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label or peel off label), immediately before dispensing the medication kit to the participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document. Sabatolimab will be administered IV. Further instructions for the preparation and dispensation of sabatolimab are described in the Pharmacy Manual.

Azacitidine (Combination cohort)

Each study site will be supplied by Novartis with the study treatment azacitidine as global or local clinical open supply and will be packed and labelled under the responsibility of Novartis. Investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label or peel off label), immediately before dispensing the medication kit to the participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document. Azacitidine may be administered i.v. or subcutaneously. For details on preparation refer to the country-specific label instructions and/or azacitidine package insert.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

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

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

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

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Participants will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.1.2 Handling of additional treatment

Not applicable.

6.7.2 Instruction for prescribing and taking study treatment

Refer to Section 6.1.1

All kits of study treatment assigned by the IRT will be recorded in the IRT system if sourced globally.

7 Informed consent procedures

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

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her level of understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

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

Novartis will provide to investigators in a separate document a proposed informed consent form, an assent form for adolescents below 18 years old at the time of enrollment, and an informed consent for parent legal guardians, that complies with the ICH E6 GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

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

The following informed consents are included in this study:

- Main study consent, which also includes:
  - A subsection that requires a separate signature for the ‘Optional Consent for Additional Research’ to allow future research on data/samples collected during this study
- As applicable, Pregnancy Outcomes Reporting Consent for female participants
- A molecular pre-screening informed consent to allow shipping of local bone marrow aspirate collected as per routine practice to a designated central laboratory for central analysis

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

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

8 Visit schedule and assessments

Assessment schedule Table 8-1 and Table 8-2 lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

- Each treatment cycle is 28 days.
- Screening evaluations should be performed within ≤ 28 days of Cycle 1 Day 1 (except for the pregnancy test which has to be performed within 72 hours before the first dose). Lab tests results must be provided within a maximum of 7 days prior to start of treatment.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1 and Table 8-2) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

During the course of the study visits, test and/or procedures should occur on schedule whenever possible. A visit window of +/- 3 days is allowed for study procedures (including treatment administration after C1D1). See Section 6.1 and Section 6.5 for details on study treatment, dosing and permitted dose delays. A visit window of +/- 7 days will be allowed for BMA procedures. Further, a maximum of 7 days is allowed between BMA efficacy, hematology assessments, and extramedullary disease assessments (if applicable) of the same visit.

Note: If a treatment cycle is delayed at any time during the study, all study visits and safety and efficacy assessments should continue according to the appropriate number of calendar days measured from Day 1 of the previous cycle, or more often if clinically indicated. In the combination cohort, when treatment is resumed, the first day of azacitidine administration will be considered as D1 of the new treatment cycle and visit schedule will be shifted accordingly. If sabatolimab administration on Day 5 is delayed within a cycle due to toxicities, visit assessments for Day 5 should be shifted accordingly.

On PK[redacted] collection days the windows and time points are provided in Section 8.5.2.

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

For post-treatment follow-up information, please refer to Section 9.1.1.2.

Table 8-1 Assessment Schedule, Sabatolimab monotherapy cohort

Period	Pre-Screening	Screening	Treatment									EOT	Safety Follow-up	Post-Treatment Follow-up
Cycle			Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7 (and subsequent cycles up to Cycle 24)			
Days	NA	-28 to -1	D1	D15	D1 ±3	D15	D1 ±3	D1 ±3	D1 ±3	D1 ±3	D1 ±3	EOT	30,90,150 days	Every 12 weeks
Pre-screening Informed Consent [1]	X													
Informed consent		X												
IRT Registration	X	X	X									X		
Demography		X												
Inclusion / Exclusion criteria		X												
AML Disease History [aHSCT and GvHD (acute and chronic) history]		X												
MRD History[2]		X												
Other relevant Medical History /Current medical conditions		X												
Prior medications (including prior antineoplastic therapies, prophylactic DLI), surgery, and medical procedures		X	continuous										X	

Period	Pre-Screening	Screening	Treatment									EOT	Safety Follow-up	Post-Treatment Follow-up
Cycle			Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7 (and subsequent cycles up to Cycle 24)			
Days	NA	-28 to -1	D1	D15	D1 ±3	D15	D1 ±3	D1 ±3	D1 ±3	D1 ±3	D1 ±3	EOT	30,90,150 days	Every 12 weeks
Physical Examination		S	S	S	S	S	S	S	S	S	S	S		
Vital Signs		X	X	X	X	X	X	X	X	X	X	X		
Body Height		X												
Body Weight		X	X		X		X	X	X	X	X	X		
Performance Status Score[3]		X	X		X		X	X	X	X	X	X		
Hematology		X	X	X	X	X	X	X	X	X	at Day1 of every cycle, and unscheduled as clinically indicated	X		every 12 weeks (aligned with the response assessments and as clinically indicated)
Chemistry		X	X	X	X	X	X	X	X	X	at Day1 of every cycle and unscheduled as clinically indicated	X		
Uric acid		X	if clinically indicated											
Coagulation		X	X				X			X	Day 1 of every 3rd cycle starting with Cycle 9 D1. Unscheduled as clinically indicated at any time.	X		
Cytogenetics [4]		X												
Urinalysis (dipstick or as per local practice)		S	if clinically indicated											
Thyroid function[5]		X					X			X	at Cycle 9 Day 1 then every 3 cycles (Day 1) thereafter and as clinically indicated	X		

Period	Pre-Screening	Screening	Treatment									EOT	Safety Follow-up	Post-Treatment Follow-up
Cycle			**Cycle 1**		**Cycle 2**		**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycle 7 (and subsequent cycles up to Cycle 24)**			
Days	**NA**	**-28 to -1**	**D1**	**D15**	**D1 ±3**	**D15**	**D1 ±3**	**D1 ±3**	**D1 ±3**	**D1 ±3**	**D1 ±3**	**EOT**	**30,90,150 days**	**Every 12 weeks**
Cytokines for safety (IFN-γ; IL-6, IL-1,TNF-α)		X	anytime for a suspected cytokine release syndrome, immediately after the AE, and one week after occurrence of AE											
Virology hepatitis B and C		S												
HIV serology (only if required per local regulation)		S												
Additional hepatic tests in case of DILI[6]		X[7]	If clinically indicated											
Serum Pregnancy test [8]		S	S[9]									S		
Urine Pregnancy Test OR Serum Pregnancy Test[8]					S		S	S	S	S	S		S (monthly)[10]	
12-Lead ECG (triplicates)		S	if clinically indicated									S		
Echocardiogram or MUGA[11]		X	if clinically indicated											
Adverse Events		X	continuous										X	
aGVHD		X	X	X	X	X	X	X	X	X	Cycle 7 Day 1 and every 2 cycles (Day1) thereafter and as clinically indicated	X	X	

Period	Pre-Screening	Screening	Treatment									EOT	Safety Follow-up	Post-Treatment Follow-up
Cycle			Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7 (and subsequent cycles up to Cycle 24)			
Days	NA	-28 to -1	D1	D15	D1 ±3	D15	D1 ±3	D1 ±3	D1 ±3	D1 ±3	D1 ±3	EOT	30,90,150 days	Every 12 weeks
cGVHD		X	X	X	X	X	X	X	X	X	Cycle 7 Day 1 and every 2 cycles (Day 1) thereafter and as clinically indicated	X	X	every 12 weeks (aligned with the response assessment and as clinically indicated)
IRT - drug dispensation (sabatolimab)			X		X		X	X	X	X	at Day 1 of each cycle until C24			
Sabatolimab infusion			X		X		X	X	X	X	at Day 1 of each cycle until C24			
Efficacy - Bone marrow aspirate or biopsy		X			X		X	X			Cycle 7 Day 1 then every 3 cycles until Cycle 13 Day 1 and then every 6 cycles including EOT until relapse or start of new therapy and as clinically indicated			
Efficacy - Extramedullary disease assessment[12]		X			X		X	X			Cycle 7 Day 1 then every 3 cycles until Cycle 13 Day 1 and then every 6 cycles including EOT until relapse or start of new therapy and as clinically indicated			
Efficacy - response assessment		X[13]			X		X	X			Cycle 7 Day 1 then every 3 cycles until Cycle 13 Day 1 and then every 6 cycles including EOT until relapse or start of new therapy and as clinically indicated			
Biomarker - Bone marrow aspirate for MRD/MFC (central)		X[14]			X		X	X			Cycle 7 Day 1 then every 3 cycles until Cycle 13 Day 1 and then every 6 cycles including EOT until relapse or start of new therapy and as clinically indicated			

Period	Pre-Screening	Screening	Treatment									EOT	Safety Follow-up	Post-Treatment Follow-up
Cycle			Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7 (and subsequent cycles up to Cycle 24)			
Days	NA	-28 to -1	D1	D15	D1 ±3	D15	D1 ±3	D1 ±3	D1 ±3	D1 ±3	D1 ±3	EOT	30,90,150 days	Every 12 weeks
[redacted]														
Biomarker - Bone marrow aspirate for phenotypic [redacted]		X[14]			X		X	X			Cycle 7 Day 1 then every 3 cycles until Cycle 13 Day 1 and then every 6 cycles including EOT until relapse or start of new therapy and as clinically indicated			
Biomarker - Peripheral blood for phenotypic [redacted]			X		X			X			Cycle 7 Day 1			
[redacted]														

Period	Pre-Screening	Screening	Treatment									EOT	Safety Follow-up	Post-Treatment Follow-up
Cycle			Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7 (and subsequent cycles up to Cycle 24)			
Days	NA	-28 to -1	D1	D15	D1 ±3	D15	D1 ±3	D1 ±3	D1 ±3	D1 ±3	D1 ±3	EOT	30,90,150 days	Every 12 weeks
Pharmacokinetic (PK) sampling[19]			X		X		X			X	at Day 1 of cycles 9, 12, 18, 24	X	at 30 and 150 days (if visit is conducted at site)	
[redacted]														
Antineoplastic therapy since discontinuation													X	X
Disposition		X									X	X		X

Period	Pre-Screening	Screening	Treatment									EOT	Safety Follow-up	Post-Treatment Follow-up
Cycle			Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7 (and subsequent cycles up to Cycle 24)			
Days	NA	-28 to -1	D1	D15	D1 ±3	D15	D1 ±3	D1 ±3	D1 ±3	D1 ±3	D1 ±3	EOT	30,90,150 days	Every 12 weeks

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Pre-screening ICF will only be applicable for participants who will be monitored by MRD testing as part of their standard of care.
[2] All local MRD assessments from BMA or peripheral blood prior to enrollment should be recorded, if available, including pre-transplant MRD assessment and post-transplant assessments until assessment used for screening.
[3] ECOG PS scale will be used for the adult cohort, Karnofsky Scale will be used for adolescents ≥ 16 years, and Lansky Scale will be used for adolescents < 16 years. Refer to Table 8-6 and Table 8-7.
[4] Cytogenetic status at diagnosis is to be recorded in the clinical database (eCRF)
[5] Any deficiency should be corrected before the start of Study Treatment. refer to Table 8-7 for details on analytes to be tested
[6] Refer to Section 6.5.5.1 for DILI follow -up
[7] Only GLDH to be tested at baseline- see Table 8-8
[8] This test will be performed only for women with child bearing potential
[9] Does not need to be performed, if it was done in screening within 72 hours before first dose
[10] Pregnancy testing for women of childbearing potential should be performed monthly during the safety follow-up period (urine or serum test may be performed, depending on local regulations
[11] A pre-existing assessment may be used if done within 6 months prior to enrollment
[12] Extramedullary disease is to be assessed via physical examination. Additional evaluation [eg, imaging, procedures (tissue biopsy, lumbar puncture), etc.] will be performed as clinically indicated per the investigator's assessment.
[13] A pre-existing assessment done as part of standard of care can used, if done within 28 days from enrollment/randomization
[14] Pre-existing bone marrow aspirate collected locally can be used, if collected within 28 days of enrollment/randomization
[15] Cryopreserved (preferred) or frozen BMA samples from initial diagnosis and pretransplant should be submitted, if available
[redacted]
[19] For adult participants PK samples will be collected only at Cycles 1, 3, 6, 24,EOT and 30 days and 150 days of the safety follow-up. For adolescent participants, additional samples will be collected at Cycles 2, 9, 12 and 18.

Period	Pre-Screening	Screening	Treatment									EOT	Safety Follow-up	Post-Treatment Follow-up
Cycle			Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7 (and subsequent cycles up to Cycle 24)			
Days	NA	-28 to -1	D1	D15	D1 ±3	D15	D1 ±3	D1 ±3	D1 ±3	D1 ±3	D1 ±3	EOT	30,90,150 days	Every 12 weeks
[redacted]														

Table 8-2 Assessment Schedule, Sabatolimab in combination with Azacitidine

Period	Pre-Screening	Screening	Treatment																EOT	Safety Follow-up
Cycle			Cycle 1			Cycle 2			Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7 (and subsequent cycles until C24)			
Days	NA	-28 to -1	D1	D5 ±3	D15 ±3	D1	D5 ±3	D15 ±3	D1	D5 ±3	D1	D5 ±3	D1	D5 ±3	D1	D5 ±3	D1	D5 ±3	EOT	30,90,150 days
Pre-screening Informed Consent [1]	X																			
Informed consent		X																		
IRT Registration	X	X	X																X	
Demography		X																		
Inclusion / Exclusion criteria		X																		
AML Disease History [aHSCT and GvHD (acute and chronic) history]		X																		
MRD History[2]		X																		
Other relevant Medical History /Current medical conditions		X																		

Period	Pre-Screening	Screening	Treatment																EOT	Safety Follow-up
Cycle			Cycle 1			Cycle 2			Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7 (and subsequent cycles until C24)			
Days	NA	-28 to -1	D1	D5 ±3	D15 ±3	D1	D5 ±3	D15 ±3	D1	D5 ±3	D1	D5 ±3	D1	D5 ±3	D1	D5 ±3	D1	D5 ±3	EOT	30,90,150 days
Prior medications (including prior antineoplastic therapies, prophylactic DLI), surgery, and medical procedures		X	continuous																	X
Physical Examination		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	
Vital Signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Body Height		X																		
BSA (use height from screening)			X			X			X		X		X		X		X			
Body Weight		X	X			X			X		X		X		X		X		X	
Performance Status Score[3]		X	X			X			X		X		X		X		X		X	
Hematology		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	at Day 1 and 5 of every cycle and unscheduled as clinically indicated		X	
Chemistry		X	X		X	X		X	X		X		X		X		at Day 1 of every cycle and unscheduled as clinically indicated		X	
Uric acid		X	if clinically indicated																	

Period	Pre-Screening	Screening	Treatment																EOT	Safety Follow-up
Cycle			Cycle 1			Cycle 2			Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7 (and subsequent cycles until C24)			
Days	NA	-28 to -1	D1	D5 ±3	D15 ±3	D1	D5 ±3	D15 ±3	D1	D5 ±3	D1	D5 ±3	D1	D5 ±3	D1	D5 ±3	D1	D5 ±3	EOT	30,90,150 days
Coagulation		X	X						X						X		Day 1 of every 3rd cycle starting with Cycle 9 D1. Unscheduled as clinically indicated at any time.		X	
Cytogenetics [4]		X																		
Urinalysis (dipstick or as per local practice)		S	if clinically indicated																	
Thyroid function[5]		X							X						X		at Cycle 9 Day 1 then every 3 cycles (Day 1) thereafter and as clinically indicated		X	
Cytokines for safety (IFN-γ; IL-6, IL-1, TNF-α)		X	anytime for a suspected cytokine release syndrome, immediately after the AE, and one week after occurrence of AE																	
Virology hepatitis B and C		S																		
HIV serology (only if required per local regulation)		S																		

Period	Pre-Screening	Screening	Treatment																EOT	Safety Follow-up
Cycle			Cycle 1			Cycle 2			Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7 (and subsequent cycles until C24)			
Days	NA	-28 to -1	D1	D5 ±3	D15 ±3	D1	D5 ±3	D15 ±3	D1	D5 ±3	D1	D5 ±3	D1	D5 ±3	D1	D5 ±3	D1	D5 ±3	EOT	30,90,150 days
Additional hepatic tests in case of DILI[6]		X[7]	If clinically indicated																	
Serum Pregnancy test [8]		S	S[9]																S	
Urine Pregnancy Test OR Serum Pregnancy Test[8]						S			S		S		S		S		S			S (monthly)[10]
12-Lead ECG (triplicates)		S	if clinically indicated																S	
Echocardiogram or MUGA[11]		X	if clinically indicated																	
Adverse Events		X	continuous																	X
aGVHD		X	X		X	X		X	X		X		X		X		Cycle 7 Day 1 and every 2 cycles (Day 1) thereafter and as clinically indicated		X	X
cGVHD		X	X		X	X		X	X		X		X		X		Cycle 7 Day 1 and every 2 cycles (Day 1) thereafter and as clinically indicated		X	X
IRT - drug dispensation (sabatolimab)				X			X			X		X		X		X		at Day 5 of each cycle until C24		

Period	Pre-Screening	Screening	Treatment																EOT	Safety Follow-up
Cycle			Cycle 1			Cycle 2			Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7 (and subsequent cycles until C24)			
Days	NA	-28 to -1	D1	D5 ±3	D15 ±3	D1	D5 ±3	D15 ±3	D1	D5 ±3	D1	D5 ±3	D1	D5 ±3	D1	D5 ±3	D1	D5 ±3	EOT	30,90,150 days
Sabatolimab infusion				X			X			X		X		X		X		at Day 5 of each cycle until C24		
IRT - drug dispensation (azacitidine)			Days 1-5 of each cycle until C24																	
Azacitidine infusion			Days 1-5 prior to sabatolimab of each cycle until C24																	
Efficacy - Bone marrow aspirate or biopsy		X				X			X		X						Cycle 7 Day 1 then every 3 cycles until Cycle 13 Day 1 and then every 6 cycles including EOT until relapse or start of new therapy and as clinically indicated			
Efficacy - Extramedullary disease assessment[12]		X				X			X		X						Cycle 7 Day 1 then every 3 cycles until Cycle 13 Day 1 and then every 6 cycles including EOT until relapse or start of new therapy and as clinically indicated			
Efficacy - response assessment		X[13]				X			X		X						Cycle 7 Day 1 then every 3 cycles until Cycle 13 Day 1 and then every 6 cycles including EOT until relapse or start of new therapy and as clinically indicated			
Biomarker - Bone marrow aspirate for MRD/MFC (central)	X[14]					X			X		X						Cycle 7 Day 1 then every 3 cycles until Cycle 13 Day 1 and then every 6 cycles including EOT until relapse or start of new therapy and as clinically indicated			

Period	Pre-Screening	Screening	Treatment																EOT	Safety Follow-up
Cycle			Cycle 1			Cycle 2			Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7 (and subsequent cycles until C24)			
Days	NA	-28 to -1	D1	D5 ±3	D15 ±3	D1	D5 ±3	D15 ±3	D1	D5 ±3	D1	D5 ±3	D1	D5 ±3	D1	D5 ±3	D1	D5 ±3	EOT	30,90,150 days
[redacted]																				
Biomarker - Bone marrow aspirate for phenotypic [redacted]		X[14]				X			X		X						Cycle 7 Day 1 then every 3 cycles until Cycle 13 Day 1 and then every 6 cycles including EOT until relapse or start of new therapy and as clinically indicated			
Biomarker - Peripheral blood for phenotypic [redacted]			X			X					X						Cycle 7 Day 1			
[redacted]																				

Period	Pre-Screening	Screening	Treatment																EOT	Safety Follow-up
Cycle			Cycle 1			Cycle 2			Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7 (and subsequent cycles until C24)			
Days	NA	-28 to -1	D1	D5 ±3	D15 ±3	D1	D5 ±3	D15 ±3	D1	D5 ±3	D1	D5 ±3	D1	D5 ±3	D1	D5 ±3	D1	D5 ±3	EOT	30,90,150 days
PK sampling for sabatolimab				X						X						X		at Day 5 of cycle 24	X	at Day 30 and 150 (if visit is conducted at site)
[redacted]																				
Antineoplastic therapy since discontinuation																				X
Disposition		X																	X	

Period	Post-Treatment Follow-up
Cycle	
Days	Every 12 weeks
Pre-screening Informed Consent [1]	
Informed consent	
IRT Registration	
Demography	
Inclusion / Exclusion criteria	

Period	**Post-Treatment Follow-up**
Cycle	
Days	**Every 12 weeks**
AML Disease History [aHSCT and GvHD (acute and chronic) history]	
MRD History[2]	
Other relevant Medical History /Current medical conditions	
Prior medications (including prior antineoplastic therapies, prophylactic DLI), surgery, and medical procedures	
Physical Examination	
Vital Signs	
Body Height	
BSA (use height from screening)	
Body Weight	
Performance Status Score[3]	
Hematology	every 12 weeks (aligned with the response assessments and as clinically indicated)
Chemistry	
Uric acid	
Coagulation	
Cytogenetics [4]	
Urinalysis (dipstick or as per local practice)	
Thyroid function[5]	
Cytokines for safety (IFN-γ; IL-6, IL-1, TNF-α)	
Virology hepatitis B and C	
HIV serology (only if required per local regulation)	
Additional hepatic tests in case of DILI[6]	
Serum Pregnancy test [8]	
Urine Pregnancy Test OR Serum Pregnancy Test[8]	
12-Lead ECG (triplicates)	
Echocardiogram or MUGA[11]	

Period	Post-Treatment Follow-up
Cycle	
Days	Every 12 weeks
Adverse Events	
aGVHD	
cGVHD	every 12 weeks (aligned with the response assessment and as clinically indicated)
IRT - drug dispensation (sabatolimab)	
Sabatolimab infusion	
IRT - drug dispensation (azacitidine)	
Azacitidine infusion	
Efficacy - Bone marrow aspirate or biopsy	Cycle 7 Day 1 then every 3 cycles until Cycle 13 Day 1 and then every 6 cycles including EOT until relapse or start of new therapy and as clinically indicated
Efficacy - Extramedullary disease assessment[12]	Cycle 7 Day 1 then every 3 cycles until Cycle 13 Day 1 and then every 6 cycles including EOT until relapse or start of new therapy and as clinically indicated
Efficacy - response assessment	Cycle 7 Day 1 then every 3 cycles until Cycle 13 Day 1 and then every 6 cycles including EOT until relapse or start of new therapy and as clinically indicated
Biomarker - Bone marrow aspirate for MRD / MFC (central)	Cycle 7 Day 1 then every 3 cycles until Cycle 13 Day 1 and then every 6 cycles including EOT until relapse or start of new therapy and as clinically indicated
Biomarker- Collection of archival BMA sample for retrospective MRD analysis	
[redacted]	
Biomarker - Bone marrow aspirate for phenotypic [redacted]	Cycle 7 Day 1 then every 3 cycles until Cycle 13 Day 1 and then every 6 cycles including EOT until relapse or start of new therapy and as clinically indicated
Biomarker - Peripheral blood for phenotypic [redacted]	
[redacted]	
PK sampling for sabatolimab	
[redacted]	

Period	Post-Treatment Follow-up
Cycle	
Days	Every 12 weeks
Antineoplastic therapy since discontinuation	X
Disposition	X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Pre-screening ICF will only be applicable for participants who will be monitored by MRD testing as part of their standard of care.
[2] All local MRD assessments from BMA or peripheral blood prior to enrollment should be recorded, if available, including pre-transplant MRD assessment and post-transplant assessments until assessment used for screening.
[3] ECOG PS scale will be used for the adult cohort, Karnofsky Scale will be used for adolescents ≥ 16 years, and Lansky Scale will be used for adolescents < 16 years. Refer to Table 8-6 and Table 8-7.
[4] Cytogenetic status at diagnosis is to be recorded in the clinical database (eCRF)
[5] Any deficiency should be corrected before the start of Study Treatment. Refer to Table 8-7 for details on analytes to be tested.
[6] Refer to Section 6.5.5.1 for DILI follow-up
[7] Only GLDH to be tested at baseline - see Table 8-8
[8] This test will be performed only for women with child bearing potential
[9] Does not need to be performed, if it was done in screening within 72 hours before first dose
[10] Pregnancy testing for women of childbearing potential should be performed monthly during the safety follow-up period (urine or serum test may be performed, depending on local regulations
[11] A pre-existing assessment may be used if done within 6 months of enrollment
[12] Extramedullary disease is to be assessed via physical examination. Additional evaluation [e.g., imaging, procedures (tissue biopsy, lumbar puncture), etc.] will be performed as clinically indicated per the investigator's assessment.
[13] A pre-existing assessment done as part of standard of care can used, if done within 28 days from enrollment/randomization
[14] Pre-existing bone marrow aspirate collected locally can be used, if collected within 28 days of enrollment/randomization
[15] Cryopreserved (preferred) or frozen BMA samples from initial diagnosis and pretransplant should be submitted, if available

[redacted]

8.1 Screening

Pre-screening sample collection

MRD testing is considered routine standard of care practice for post-transplant participants, and therefore it is expected that these tests would be performed irrespective of participant's trial participation.

The participants enrolled on this study will have undergone post-transplant MRD testing on blood or bone marrow aspirate samples and participant's eligibility for the study will be based on the MRD results from the site local laboratory (or central assessment where required (e.g US)). A bone marrow aspirate (BMA) sample must be provided for central MRD testing for all participants entering the study. The collection and shipment of this BMA sample for central MRD testing may occur before screening (= pre-screening collection) or during screening (= screening collection).

- Pre-screening collection occurs when a BMA sample is collected and shipped before local MRD status is known (e.g. in order to avoid repeating unnecessarily the bone marrow aspiration procedure, the BMA samples for local and central MRD tests can be collected during the same procedure and the BMA sample for central MRD testing can be shipped straight away, before local MRD status is known, this is in order to preserve sample integrity). In this case, the participant will have to sign the pre-screening ICF before the sample is collected and shipped to the central laboratory and the participant will then have the opportunity to sign the screening ICF if the local MRD status is confirmed as positive. Note that it is possible that, under the pre-screening ICF, a participant will go through several local MRD tests (and hence potentially several collections and shipments of BMA sample for central MRD testing) before a positive MRD status is obtained locally.
- Screening collection occurs when a BMA sample for central MRD testing is shipped after the MRD positive status was obtained by local assessment (e.g. local MRD positive status was obtained on blood and the BMA collection/shipment occurs thereafter, during screening). In this case, the participant will not sign the pre-screening ICF but will sign the screening ICF directly after MRD positivity was confirmed locally.

  For sites in the USA where central assessment is required, screening collection occurs when a BMA sample for central MRD testing is shipped directly to the central lab.

Screening

All participants must provide signed ICFs prior to performing any study specific procedures. Screening assessments to confirm eligibility should be performed as per the schedule of assessments detailed in Table 8-1 and Table 8-2. participants will be evaluated against all study inclusion and exclusion criteria and safety assessments which must be completed within 28 days prior to the start of study treatment (C1D1), with the exception of the local serum pregnancy test (for women of child-bearing potential) which must be conducted and confirmed as negative within 72 hrs prior to the start of study treatment. Lab test results must be provided within a maximum of 7 days prior to study treatment. Laboratory parameters may be retested within the

28-day screening period. If the repeat value remains outside of the specified ranges, the participant will be considered a screen failure.

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

8.1.1 Eligibility screening

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

8.1.2 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible prior to administration of study treatment (C1D1) will be considered a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form (CRF). The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see Section 10.1.3 for reporting details). If the participant is screen failed or will not be treated, the IRT is to be notified within 2 days e that the participant was not enrolled.

8.2 Participant demographics/other baseline characteristics

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

- Disease history, including date of diagnosis, 2016 World Health Organization (WHO) AML classification (Arber et al 2016), ELN cytogenetic risk stratification (Döhner et al 2017), and any additional molecular markers (FLT3-TKD, isocitrate dehydrogenase 1 and 2 (IDH1/2), DNMT3A, c-KIT, and others) (National Comprehensive Cancer 2020). Refer to Appendix 5 Section 16.5 for details.
- Prior antineoplastic therapies [prior to aHSCT and post-aHSCT (before start of study treatment) including prophylactic donor lymphocyte infusion(s) with or without HMAs].
- aHSCT characteristics, conditioning regimen intensity, disease remission status at transplant (e.g., CR with undetectable MRD, CR with detectable MRD, active disease), timing of transplant (e.g., first CR, second CR, outside of CR2, refractory / induction failure), prior and current history of aGvHD or cGvHD, immunosuppressive therapy (systemic GvHD prophylaxis or treatment, date of completion).
- Race/ethnicity (participant race /ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities)
- All prior and concomitant medications and medical procedure
- Results, timing, and methods used for local MRD assessment.

Other assessments will be completed for the purpose of determining eligibility for inclusion in the study as reported in Table 8-1 and Table 8-2.

Assessments to be performed at screening include:

- After all study ICFs are signed the participant will be registered with the IRT
- Inclusion/exclusion criteria
- Medical history/current medical conditions
- Disposition
- Physical examination
- ECOG Performance Status, body height, weight, vital signs (blood pressure (supine position preferred when ECGs are collected) and pulse, and body temperature).
- Laboratory - hematology, blood chemistry, uric acid, coagulation, urinalysis, serum pregnancy test for women of child-bearing potential, thyroid function, virology hepatitis B and C, HIV serology (only if required per local regulation)
- Triplicate 12-lead local ECG
- Echocardiogram/MUGA, if not performed within 6 months of enrollment
- Bone marrow aspirate collection for MRD and other biomarkers (if no sample was collected at pre-screening)
- MRD history- methodology [Flow cytometry, NGS, qPCR, chimerism] and source (BM/PB) date and results
- Bone marrow biopsy / aspirate for efficacy assessment (if no sample was collected at pre-screening)
- Extramedullary disease assessment (See Section 8.3.1)
- Blood sample for Cytokines
- Adverse events
- Blood should be collected for phenotypic assessment

8.3 Efficacy

8.3.1 Efficacy response assessment

Response assessments (bone marrow aspirate (BMA)/bone marrow biopsies (BMB)), peripheral blood, hematology assessments, extramedullary disease assessments) will be performed locally, by the Investigator, according to the assessment schedule depicted in Table 8-1 and Table 8-2 for assessment of relapse; complete remission, or complete remission with incomplete hematologic recovery.

Bone marrow assessments will be performed at screening, and pre-dose on C2D1, C3D1, C4D1 and C7D1 and every 3 cycles D1 until Cycle 13 D1 and then every 6 months and as clinically indicated until relapse, start of a new anti-neoplastic treatment, death, lost to follow-up or withdrawal of consent.

For sabatolimab monotherapy cohort participants, hematology assessments will be performed at screening, and pre-dose on D1 and D15 for the two first cycles and thereafter at D1 of each

cycle, at the end of treatment visit, at unscheduled visit as clinically indicated, and every 12 weeks for participants who enter post-treatment follow-up.

For sabatolimab in combination with azacitidine cohort participants, hematology assessments will be performed at screening, and pre-dose on D1, D5 and D15 for the two first cycles and thereafter on D1 and D5 of each cycle, at the end of treatment visit, at unscheduled visit as clinically indicated, and every 12 weeks for participants who enter post-treatment follow-up.

Response evaluation will be based on the Investigator's assessment based on standardized criteria as proposed by the International Working Group (IWG) and European Leukemia Network (ELN) for AML (Cheson et al 2003, Döhner et al 2017) (see Table 8-1 and Table 8-2). Disease classification at baseline and evaluation of response during study treatment will rely on bone marrow, peripheral blood assessment, as well as the presence or absence of extramedullary disease. For disease characterization at baseline, the last assessment of bone marrow (within 28 days before study treatment starts) and peripheral blood counts (within 14 days before study treatment starts) at the screening visit should be used. In case of missing data for the full assessment required to qualify for a given response, the overall assessment "unknown" will be assigned unless relapse was seen in at least one compartment (i.e. bone marrow or blood, or appearance of extramedullary disease).

Extramedullary disease assessment is performed via physical examination. Additional evaluation for extramedullary disease [eg, imaging, procedures (tissue biopsy, lumbar puncture), etc.] will be performed as clinically indicated per the investigator's assessment. Cerebrospinal fluid assessment and relevant imaging techniques may be performed, as clinically appropriate at the investigator's discretion, in case of symptoms suggestive of meningeosis leukemia, and/or prior history of central nervous system involvement with AML. In case of extramedullary disease (re-) appearance during the study, the lesions should be considered for confirmation by imaging or biopsy if technically and/or clinically feasible.

Assessment for the presence or absence of extramedullary disease will be performed at screening, and pre-dose on C2D1, C3D1, C4D1 and C7D1 and every 3 cycles D1 until Cycle 13 D1 and then every 6 months and as clinically indicated until relapse, start of a new anti-neoplastic treatment, death, lost to follow-up or withdrawal of consent. The presence or absence and physical location of extramedullary disease are to be recorded on the CRFs.

Participants can be assessed for disease response (bone marrow assessment, hematology, extramedullary disease assessment) at any time if clinically indicated, for example in case of suspicion of relapse. Therefore, more frequent efficacy assessments may be performed at the investigator's discretion, if medically indicated, and recorded as an unscheduled visit in the eCRFs. Clinical suspicion of relapse at any time will require an evaluation promptly, rather than waiting for the next scheduled assessment. In case of an unscheduled or delayed disease evaluation of any reason, subsequent assessments should be performed according to the originally planned schedule.

More frequent efficacy assessments, performed at the Investigator's discretion, should be recorded on the Unscheduled Visit CRFs. All assessments will be analyzed.

Table 8-3 Response classification in AML at a given evaluation time (based on IWG Cheson et al 2003, ELN 2017 Döhner et al 2017)

Response Category	Definition[1]
Complete Remission	• Bone marrow: blasts < 5% • Peripheral blood: No circulating blasts or blasts with Auer rods • No evidence of extramedullary disease (such as CNS or soft tissue involvement) • Neutrophils ≥ $1.0x10^9$/L • Platelets ≥ $100x10^9$/L
Complete remission with incomplete hematologic recovery (CRi)	• Bone marrow: blasts < 5% • Peripheral blood: No circulating blasts or blasts with Auer rods • No evidence of extramedullary disease (such as CNS or soft tissue involvement) • Neutrophils < $1.0x10^9$/L or platelets < $100x10^9$/L
Hematologic relapse (from CR or CRi)	Only in participants with CR or CRi. Any of the following: • Reappearance of blasts in peripheral blood **OR** • Bone marrow blasts ≥ 5% **OR** • Development of extramedullary disease
Unknown	In case the response assessment was not done, or the assessment was incomplete

[1] If not defined otherwise, all of these criteria apply

Post treatment efficacy follow up

Participants who discontinue treatment for reasons other than documented relapse from CR/CRi, death, lost to follow-up, or withdrawal of consent, will enter the post-treatment follow-up phase (Section 9.2). Hematology assessments must continue to be performed every 3 months, response should be assessed at least every 6 months, and bone marrow assessment should be done at least every 6 months until relapse or start of new therapy per Table 8-1 and Table 8-2, or as clinically indicated any time in case relapse is suspected.

The post-treatment follow-up period will last until participant's documented relapse (per ELN criteria (Döhner et al 2017), see Table 8-1 and Table 8-2, start of new therapy, death, lost to follow-up, or withdrawal of consent or the end of study whichever comes first.

8.3.2 Efficacy assessment: MRD by MFC

MRD in bone marrow will be assessed by central multi-parameter flow cytometry (MFC). Assessments will be performed at baseline, and during the treatment period until relapse, as indicated in the table below. The first volume aspirated from the bone marrow should be provided for this assessment, when possible.

MRD-negative will be defined based on the detection of Leukemia associated immunophenotype (LAIP), at a threshold defined by the AML-MRD flow cytometry assay.

[redacted]

A cryopreserved bone marrow aspirate sample performed at diagnostic and prior aHSCT is requested for retrospective MRD analysis (if available). The sample should be submitted at C1D1 after the participant is confirmed to have received his/her first dose. The BMA samples will be used to determine the presence of LAIP at diagnostic and prior aHSCT, as well as additional relevant biomarkers and genetic alterations related to AML.

Table 8-4 BMA for MRD by flow cytometry

Volume of BMA / visit	Visit*	Time Point
Cryopreserved / frozen archival diagnostic sample**	Screening**	Anytime
Cryopreserved / frozen archival pre-transplant sample**	Screening**	Anytime
4mL (First BMA draw should be provided for this assessment)	Screening or prescreening***	Anytime
	C2D1	Pre-study treatment dose
	C3D1	Pre-study treatment dose
	C4D1	Pre-study treatment dose
	C7D1	Pre-study treatment dose
	C10D1	Pre-study treatment dose
	C13D1	Pre-study treatment dose
	Every 6 cycles after cycle 13 D1 (including EOT and post-treatment follow up) until relapse**** or start of new therapy and as clinically indicated	Pre-study treatment dose, if applicable
	Unscheduled*****	Anytime

* Collection of BMA samples for biomarkers should be performed at same time as bone marrow collection for disease assessment/efficacy at the indicated timepoints.
** If available, sites should provide archival cryopreserved (preferred) / frozen bone marrow aspirate MRD samples collected at initial diagnosis and prior to aHSCT. For further details on sample collection please refer to the [CMBG453F12201 Laboratory Manual].
*** Prescreening fresh BMA sample can be used, if collected within 28 days from randomization/enrollment.
****If a participant is MRD+ at end of study treatment no MRD collection will be required during post-treatment follow up.
***** In rare occasions scheduled samples and/or additional samples can be collected outside of planned visits.

8.3.3 Appropriateness of efficacy assessments

The assessment of response to study treatment is based on standardized criteria as proposed by the European LeukemiaNet (ELN) and the International Working Group (IWG) (Cheson et al 2003, Döhner et al 2017) in Table 8-3.

8.4 Safety

Safety assessments are specified in Table 8-5 below with the assessment schedule detailing when each assessment is to be performed.

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

Table 8-5 Assessments & Specifications

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A complete physical examination is required at screening, D1 and D15 for the first 2 cycles (C1 and C2) and thereafter at D1 of each cycle until EOT. For **sabatolimab in combination with azacitidine Cohort**: At screening, D5 and D15 for the 2 first cycles (C1 and C2) and thereafter at D1 of each cycle until EOT. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature are collected at screening, D1 and D15 for the first 2 cycles (C1 and C2) and thereafter at D1 of each cycle until EOT (Cohort 1) For **sabatolimab in combination with azacitidine Cohort** vital signs will be collected at screening, D1, D5 and D15 for the two first cycles (C1 and C2) and thereafter at D1 and D5 of each cycle until EOT.
Height and weight	Height in centimeters (cm) will be measured at Screening. Body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 8-1 and Table 8-2

Performance status:

ECOG Performance status scale will be used for the adult cohort as described in Table 8-6, and Karnofsky/Lansky Performance Scales will be used for the adolescent cohort as described in Table 8-7.

Table 8-6 ECOG performance status

Grade	ECOG Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

Grade	ECOG Status
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Death

Table 8-7 Karnofsky/Lansky Performance Scales

Karnofsky Scale (age ≥ 16 years)		Lansky Scale (age < 16 years)	
Able to carry on normal activity and to work; no special care needed.		Able to carry on normal activity; no special care is needed	
100	Normal no complaints; no evidence of disease	**100**	Fully active
90	Able to carry on normal activity; minor signs or symptoms of disease	**90**	Minor restriction in physically strenuous play
80	Normal activity with effort; some signs or symptoms of disease	**80**	Restricted in strenuous play, tires more easily, otherwise active
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.		Mild to moderate restriction	
70	Cares for self; unable to carry on normal activity or to do active work	**70**	Both greater restrictions of, and less time spent in active play
60	Requires occasional assistance, but is able to care for most of his personal needs	**60**	Ambulatory up to 50% of the time, limited active play with assistance/supervision
50	Requires considerable assistance and frequent medical care	**50**	Considerable assistance required for any active play, fully able to engage in quiet play
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.		Moderate to severe restriction	
40	Disabled; requires special care and assistance	**40**	Able to initiate quiet activities
30	Severely disabled; hospital admission is indicated although death not imminent	**30**	Needs considerable assistance for quiet activity
20	Very sick; hospital admission necessary; active supportive treatment necessary	**20**	Limited to very passive activity initiated by others (e.g. television)

Karnofsky Scale (age ≥ 16 years)		Lansky Scale (age < 16 years)	
10	Moribund; fatal processes progressing rapidly	**10**	Completely disabled, not even passive play
0	Dead	**0**	Unresponsive

8.4.1 Laboratory evaluations

Local clinical laboratory parameters will be used for the analysis of scheduled hematology, chemistry and other blood specimens collected as part of safety monitoring (as detailed in Table 8-1 and Table 8-2 and Table 8-8) and the results will be collected in the eCRF.

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

A central laboratory will be used for the parameters listed in Table 8-9 and as per the schedule in Table 8-1 and Table 8-2.

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

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

Table 8-8 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hemoglobin (Hgb), white blood cells (WBC), differential (including basophils, eosinophils, lymphocytes, monocytes, neutrophils, bands, metamyelocytes, myelocytes, promyelocytes, blasts), atypical cells (e.g. LUC, erythroblasts), platelets (absolute value preferred, %s are acceptable)
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphorus, Sodium, Potassium, Bicarbonate, Creatinine, Creatine kinase, Total Bilirubin, (Indirect Bilirubin, Direct Bilirubin) *, Total Cholesterol, Total Protein, Blood Urea Nitrogen (BUN) or Urea, Amylase, Lipase, Glucose (fasting), Troponin-T or Troponin I, CRP, NTproBNP**
Chemistry	Uric acid
Virology***	HBsAg, HBcAb, HBV DNA (in participants positive for HBcAb), HCV RNA (PCR) HIV (Only if required by local regulation)
Coagulation	International normalized ratio [INR]), Activated partial thromboplastin time (APTT), fibrinogen
Thyroid	At baseline: TSH, Free-T3 and Free-T4. During treatment: TSH at time points indicated in Table 8-1 and Table 8-2 and as clinically indicated. If TSH is abnormal, then test free-T3 and free-T4
Urinalysis*** (dipstick and sediment)	Dipstick examination includes specific gravity, pH, glucose, protein, blood, bilirubin, ketones and WBC as clinically indicated.

Test Category	Test Name
Pregnancy Test***	Serum / Urine pregnancy test (refer to Section 8.4.3) 'Pregnancy and assessments of fertility'

* Indirect and direct bilirubin only required if total bilirubin is abnormal
** NTproBNP may be required as an additional test upon signs/symptoms and based on cardiology consult
*** Virology, urinalysis, and pregnancy test will only be reported in the source documentation

Table 8-9 Central clinical laboratory parameters collection plan

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

[1] at baseline and as clinically indicated for follow-up of DILI per Section 6.5.5.1

8.4.2 Electrocardiogram (ECG)

Standard triplicate 12 lead ECG recording will be performed according to Table 8-10. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

The ECGs are to be collected with local ECG machines at the time points indicated in the ECG collection plan Table 8-10 .

Table 8-10 ECG collection plan

Cycle	Day	Time point
Screening	Day -28 to Day -1	Anytime
EOT	N/A	Anytime
Unscheduled	Any	As clinically indicated[1]

* all ECGs to be collected in 12-lead triplicate
[1] ECG collection prior to any study drug dosing

All ECGs must be recorded using the local machine.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated and reported as unscheduled time points.

Interpretation of the tracing must be made by a qualified physician and documented in the source documents. Each ECG tracing should be labeled with the study number, participant initials (where regulations permit), participant number, date, and kept in the source documents at the study site.

Clinically significant abnormalities present at screening should reported on the Medical History CRF. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

In case of QTcF prolongation, please refer to Section 6.5.5.3.

8.4.2.1 Echocardiogram or MUGA

The left ventricular cardiac function will be evaluated by echocardiogram or MUGA at baseline according to the visit schedule in Table 8-1 and Table 8-2 and if clinically indicated.

8.4.3 Pregnancy and assessments of fertility

Females of child-bearing potential are defined as all females physiologically capable of becoming pregnant. This includes female pediatric participants who are menarchal or who become menarchal during the study.

All menarchal girls and their parents/caregivers should be informed about the potential risks of pregnancy and the need to prevent pregnancy during the study.

It is important to be sensitive in introducing this issue, as understanding and comprehension of puberty, sexual activity, pregnancy and contraception is influenced by age, as well as factors such as precocity, socio (educational) economic and familial background. These discussions with the participant and her parents/caregivers are therefore best performed by investigators familiar with the pediatric participant and her family and should be guided by requirements of the local regulatory authorities. These discussions should take into account the socio-economic, cultural factors and religious beliefs of the adolescent participant and her family. The investigator should also discuss the management of the pregnancy test results with the participant and her parents/caregivers. The privacy of the participant should be considered in accordance with the local law and ethics.

Participants becoming pregnant must be discontinued from study drug.

However, a participant may choose to remain in the study should she become pregnant and be followed according to the protocol-defined study visits.

Serum pregnancy test will be performed for all females of child-bearing potential according to the protocol assessment schedule below:

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

During the study, a urine/serum pregnancy test should be performed at Day 1 of each cycle (except Cycle 1 if a pregnancy test had been performed within 72 hours of the first dose) and a serum pregnancy test at EOT visit. Pregnancy testing (urine/serum) should occur at monthly intervals during the 150-day safety follow-up period. Refer to Table 8-1 and Table 8-2 for pregnancy testing schedule. Additional pregnancy testing might be performed if requested by local requirements or at investigators discretion. A positive urine pregnancy needs to be confirmed with a serum test. Confirmed positive pregnancy test requires immediate discontinuation of study treatment and discontinuation from study. See Section 10.1.4 for pregnancy reporting. The pregnancy tests will be recorded only in the source documentation, not in the CRF.

Assessments of fertility

Women of childbearing potential should employ the use of highly effective contraception during study treatment for 150 days after the last dose of sabatolimab and 90 days after the last

dose of azacitidine (sabatolimab with azacitidine combination Cohort). Highly effective contraception methods are defined in Section 5.2.

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

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

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

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

8.4.4 Other safety evaluations

8.4.4.1 aGvHD assessment

aGvHD staging and grading will be performed by the Investigator at screening, every 2 weeks for the first two cycles, at Day 1 visit of every cycle up to Cycle 7, then at Day 1 visit every 2 cycles during the treatment period, at EOT visit, at the Safety Follow-up visits, and as clinically indicated thereafter as outlined in Table 8-1 and Table 8-2.

aGvHD will be performed using standard criteria (Harris et al 2016): measures of body surface area aGvHD skin rash, stool volumes or frequency per 24h time period, and serum bilirubin levels, staging by organ (skin; liver; upper GI; lower GI) and overall grading at the time of the evaluation should be reported according to Appendix 1.

The data should be entered in the appropriate CRFs.

In addition, Investigator should record and report any management action of aGvHD in appropriate CRF(s).

Note: Additional aGvHD assessments (including biopsy of the organ involved) may be done as per institutional guidelines at investigator's discretion. aGvHD assessments performed at unscheduled visit and leading to a change in patient's management after the last dose of study treatment should be recorded in the CRF.

8.4.4.2 cGvHD assessment

Occurrence of definitive and possible manifestations of cGvHD will be assessed by the Investigator at screening, every two weeks for the first two cycles, at Day 1 visit of every cycle up to Cycle 7, then at Day 1 visit every 2 cycles during the treatment period, and at EOT visit.

After EOT, participants will be assessed for occurrence of cGvHD at the Safety Follow-Up visit, and at Day 30, at Day 90 and at Day 150 and every 12 weeks during the Post Treatment

follow-up period (see Table 8-1 and Table 8-2). Occurrence of cGvHD will be reported on appropriate specific CRF.

Investigator will assess cGvHD as per NIH consensus guidelines for cGvHD (Appendix 2): overall grading (mild, moderate, severe) at the time of cGvHD diagnosis which will be reported in corresponding CRF.

Additional cGvHD assessments (including biopsy of the organ involved) may be done as per institutional guidelines at investigator's discretion.

In addition, Investigator should indicate if a systemic treatment is initiated for cGvHD in appropriate CRF(s).

8.4.5 Appropriateness of safety measurements

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

Additionally, given the unique clinical setting and limited information about the use of sabatolimab in the post-aHSCT setting, additional evaluations are required:

The primary purpose of the current study is to test the hypothesis whether preemptive treatment with sabatolimab, alone or in combination, when administered to participants with AML/secondary AML who are in complete remission with MRD+ post-aHSCT, can enhance the GvL response and prevent or delay hematologic relapse. However, a sabatolimab-mediated enhancement of GvL could potentially exacerbate GvHD, an immune-mediated toxicity and a principal safety concern in the aHSCT setting.

There are no reported data on the safety of sabatolimab in the post-aHSCT setting, therefore a key primary safety objective will be to assess the occurrence and severity of treatment-emergent aGvHD and cGvHD, immune-related and other adverse events.

The study will start with a Safety Run-in to assess whether sabatolimab can be administered in the post-aHSCT setting without unacceptable levels of treatment-emergent toxicities (dose limiting toxicities, i.e.; primary safety objective), including increased or worsening the risk of treatment emergent aGvHD or cGvHD, as well as severe immune-related toxicity after 2 cycles of study treatment. The Safety Run-in will be conducted starting with a lower sabatolimab dose (i.e., 400 mg IV Q4W) than what is currently being used in the MDS and AML setting outside of aHSCT setting (i.e., 800 mg IV Q4W). If unacceptable toxicities were not observed, dose escalation at 800 mg IV Q4W will subsequently be evaluated. Details on dose escalation guidelines and determination of the recommended dose for expansion are provided in Section 6.5.

Sabatolimab will then be evaluated in Part 2 at the determined dose as monotherapy and in combination with azacitidine, as well as in adolescent participants.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

Not applicable

8.5.2 Pharmacokinetics

Pharmacokinetic (PK), [redacted] samples will be obtained and evaluated in all participants. Please refer to Table 8-11 and Table 8-12 for details on PK, [redacted] sample collections. If participants experience an SAE or an AE leading to the discontinuation of the study treatment, an unscheduled PK blood sample should be obtained as close as possible to the event occurrence. The date and time of the last dose and the time of PK blood draw should be recorded. [redacted]

8.5.2.1 Pharmacokinetic blood collection and handling

Sabatolimab PK, [redacted] blood sampling schedule is outlined in Table 8-11 and Table 8-12. Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein opposite to the arm used for infusion. A single blood sample of approximately 5 mL will be collected. After clotting, the resulting serum will be separated in aliquots and will be stored frozen until analysis. The exact date and clock times of drug administration and blood draw for PK, [redacted] assessment will be recorded on the appropriate eCRF.

After permanent discontinuation of sabatolimab, the samples scheduled for pre-sabatolimab infusion and end of sabatolimab infusion (within 2 hours) should no longer be collected.

Refer to the [CMBG453F12101 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK, [redacted] samples.

Table 8-11 Blood (serum) collection schedule for PK, [redacted] for sabatolimab monotherapy (All cohorts except Cohort 3)

Cycle	Day	Scheduled Time Point	PK sample	[redacted]
1	1	Pre-sabatolimab infusion/0h	x	
1	1	End of sabatolimab infusion (within 2 hours)	x	
2*	1	Pre-sabatolimab infusion	x	
3	1	Pre-sabatolimab infusion	x	

Cycle	Day	Scheduled Time Point	PK sample	[redacted]
3	1	End of sabatolimab infusion (within 2 hours)	x	
6	1	Pre-sabatolimab infusion	x	
9*	1	Pre-sabatolimab infusion	x	
12*	1	Pre-sabatolimab infusion	x	
18*	1	Pre-sabatolimab infusion	x	
24	1	Pre-sabatolimab infusion	x	
24	1	End of sabatolimab infusion (within 2 hours)	x	
EOT		Anytime	x	
Unscheduled or Unplanned		Anytime	x	
Follow-up day 30		Anytime	x	
Follow-up day 150		Anytime	x	

* Additional samples to be collected only for adolescent participants (Cycles 2, 9, 12 and 18)

Table 8-12 Blood (serum) collection schedule for PK, [redacted] for sabatolimab in combination with azacitidine (Cohort 3)

Cycle	Day	Scheduled Time Point	PK sample	[redacted]
1	1	Pre-HMA infusion		
1	5	Pre-sabatolimab infusion/0h	x	

Cycle	Day	Scheduled Time Point	PK sample
1	5	End of sabatolimab infusion (within 2 hours)	x
3	5	Pre-sabatolimab infusion	x
3	5	End of sabatolimab infusion (within 2 hours)	x
6	5	Pre-sabatolimab infusion	x
24	5	Pre-sabatolimab infusion	x
24	5	End of sabatolimab infusion (within 2 hours)	x
EOT		Anytime	x
Unscheduled or Unplanned		Anytime	x
Follow-up day 30		Anytime	x
Follow-up day 150		Anytime	x

8.5.2.2 Analytical method

Bioanalysis for pharmacokinetic studies will employ several validated assays:

- The assay to quantify sabatolimab will be a validated liquid chromatography mass spectrometry (LC-MS) assay.
- For further details on sample collection and processing please refer to the [CMBG453F12201 Laboratory Manual].

8.5.3 Biomarkers

The biomarker strategy for this study is (i) to monitor the persistence of malignancy at orders of magnitude below the limit of conventional morphologic detection (Section 8.3.2); (ii) to

explore mechanisms of action of sabatolimab; (iii) and finally to enhance the understanding of the biology behind the treatment response.

[redacted]

Samples will be collected at baseline, during treatment, at EOT and anytime during treatment and/or follow up period as clinically indicated, as defined in the VES (Table 8-1 and Table 8-2) and Table 8-13. BMA samples for biomarkers should always be collected at the same time as investigator assessment of disease and should preferentially be part of the first or the second draw to ensure sufficient and adequate material for analysis. All assessments will be performed at Novartis designated laboratories. In addition, the biomarker samples may be used to develop a biological test (such as a test to assess residual disease). Instructions for collection, preparation and shipment of all biomarker samples can be found in the laboratory manual. Required sample collection information must be entered on the requisition forms.

Table 8-13 BMA for Biomarkers for all cohorts

Volume of BMA for phenotypic [redacted] assessments / visit	**Visit***	**Time Point**
4 mL	Screening**	Anytime
	C2D1	Pre-dose
	C3D1	Pre-dose
	C4D1	Pre-dose
	C7D1	Pre-dose
	Every 3 cycles D1 after C7D1 until C13D1	Pre-dose
	Every 6 cycles D1 after cycle 13 D1 until relapse*** or start of new therapy (including posttreatment follow up)	Pre-dose, where applicable
	EOT	Anytime
	As clinically indicated (At same time as BM collection for efficacy)	Anytime
	Unscheduled****	Anytime

*Collection of BMA samples for biomarkers should be performed at same time as bone marrow collection for disease assessment/efficacy at the indicated time points.
** Pre-exitisting sample collected within 28 days of enrollment/randomization is acceptable
*** If a participant is MRD+ at end of study treatment no MRD collection will be required.
**** In rare occasions scheduled samples and/or additional samples can be collected outside of planned visits.

[redacted]

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

Discontinuation of study treatment will occur when a participant has documented relapse from CR/CRi or until for any of the reasons described below, and can be initiated by either the participant or the investigator.

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

Study treatment must be discontinued under the following circumstances:

- participant/guardian decision
- Pregnancy

- Use of prohibited treatment as per recommendations in the prohibited treatment (Section 6.2.2)
- Any situation in which study participation might result in a safety risk to the participant
- Any adverse events or laboratory abnormalities that in the judgment of the investigator, taking into consideration the participant's overall status, prevents the participant from continuing the study treatment
- Protocol-defined reasons for treatment discontinuation (see Section 6.1.4 and Section 6.1.5)
- Termination of the study by Novartis

If discontinuation of study treatment occurs due to circumstances other that the protocol defined criteria in Section 6.1.4 and Section 6.1.5, the investigator should make a reasonable effort to understand the primary reason for the participant's premature discontinuation of study treatment and record this information.

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see 'Withdrawal of Informed Consent' Section 9.1.2). **Where possible, they should return for the assessments indicated in the Assessment Schedule**. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

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

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

- Concomitant treatment
- Adverse events/ Serious Adverse Events

For details on AE/SAE reporting, please refer to Section 10.1.1. Information about concomitant treatment should be collected for up to 30 days after last dose of any study treatment.

In addition, for women with child-bearing potential, a serum or urine pregnancy test must be performed as indicated in Section 8.4.3.

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

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

9.1.1.1 Safety Follow-up

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

After the 30-day on-site safety follow-up visit, participants will be followed via telephone call (or onsite visit if participant happens to be visiting the site) at 90 and 150 days after the last dose of sabatolimab. All safety assessments should be completed as per Table 8-1 and Table 8-2 (Section 10.1.2). However, if the participant begins new anti-neoplastic medication before the end of the safety follow-up period the collection of new SAEs and AEs unrelated to study medication will stop and thereafter only suspected AEs and suspected SAEs will continue to be collected up to the end of the safety follow-up period. Suspected SAEs will continue to be collected beyond the 150-Day safety visit (in Post-Treatment follow-up) see. For female participants of childbearing potential, a pregnancy test will be performed at the time points listed in Table 8-1 and Table 8-2.

9.1.1.2 Post-Treatment Follow-up

All participants who discontinued study treatment while in remission without evidence of hematologic relapse will enter a post-treatment follow-up until hematologic relapse or start of new therapy. Additionally, participants with MRD- status at end of treatment will continue to be assessed for MRD until MRD+ or for 12 months after end of study treatment, whichever is earlier. Efficacy assessments must continue to be performed as per the assessment schedule (Table 8-1 and Table 8-2) with hematological assessments every 3 months (12 weeks), cGvHD assessments every 3 months (12 weeks), and bone marrow assessments every 6 months.

9.1.1.3 Replacement policy

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

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

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

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

and

- No longer wishes to receive study treatment

and

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

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

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

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

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

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

All efforts should be made to complete the assessments prior to study discontinuation. If the participant agrees, a final evaluation at the time of the participant's study discontinuation and withdrawal of consent/ opposition to use data/biological samples should be made as detailed in the assessment table (Section 8).

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

9.1.3 Lost to follow-up

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

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible to perform their End of Treatment Visit (EOT) and the assessments for EOT as described in Section 8 and will be treated as a prematurely withdrawn participant. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

In the event that the study is terminated prematurely, e.g., due investigator recommendation at the safety review meeting or Novartis decision, participants still receiving study treatment and who, according to investigator assessment, continue to benefit from the treatment, will be offered to continue study treatment as per protocol or through an alternative setting (see Section 9.2).

9.2 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

Following completion of the treatment period all participants will complete the safety follow up period, and in addition participants who are in CR/CRi will be followed for efficacy during the post-treatment follow up period for up to 12 months or until relapse, whichever occurs earlier (see Section 9.1.1.2).

The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the participant should be recorded in the source documentation.

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

The end of study is defined as all participants having completed the safety and posttreatment follow up (if applicable), or having died, been lost to follow-up or having withdrawn consent to further participation in the study.

At the end of the study, every effort will be made to continue the provision of sabatolimab outside this study through an alternative setting for participants who are still receiving treatment with sabatolimab and deriving clinical benefit in the opinion of the investigator; safety will be monitored and reported to Health Authorities as per regulatory requirements.

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

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

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

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

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

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

1. The Common Toxicity Criteria (CTC) AE grade (CTCAE version 5.0) will be used for grading of all adverse events except for GvHD (Harris 2016 for aGvHD and NIH consensus criteria for cGvHD).
2. its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment

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

- Dose not changed
- Dose reduced/increased
- Drug interrupted/withdrawn

6. its outcome

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity.

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

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

Adverse event monitoring should be continued for at least

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

OR

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

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

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

Disease hematologic relapse / progression (including fatal outcomes), if documented by use of appropriate method [for example, as per ELN 2017 (Döhner et al 2017)], should not be reported as an adverse event. Adverse events separate from the disease hematologic relapse / progression (i.e., deep vein thrombosis at the time of hematologic relapse / progression or hemoptysis concurrent with finding of disease hematologic relapse / progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

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

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

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participants with the underlying disease.

10.1.2 Serious adverse events

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

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity

- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the participant's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

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

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

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

All reports of intentional misuse and abuse of the product are also considered serious adverse events irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until the end of the safety follow-up period (Section 9.1.1.1 must be reported to Novartis safety immediately, without undue delay, under no circumstances later than within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

SAE reporting timeframes:

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

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

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

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

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

Any SAEs experienced after the participants have completed the safety follow-up period should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

10.1.4 Pregnancy reporting

Pregnancies

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

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

Pregnancy data will not be collected from the female partners of any male participants who took study treatment in this study.

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

10.1.5 Infection reporting

Infections will be reported as adverse events and the AE severity grade will be assessed according to CTCAE grading as defined in Section 10.1.

In addition, Investigators will detail the type of infection as well as the method of diagnosis and assess the event according to the Infection Severity grading (BMT CTN 2013) (Appendix 4).

10.1.6 Reporting of study treatment errors including misuse/abuse

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

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

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

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

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

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

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

10.2 Additional Safety Monitoring

Implementation of safety monitoring committees will not be required for this study considering that it is an open-label study. However, close monitoring of safety is planned; specifically, Novartis and the study investigators involved in the safety run-in will conduct at least one safety review meeting for safety run-in cohorts 1, 2 and 5 : once all evaluable participants in that cohort are observed for at least 2 cycles of treatment or experienced a DLT, whichever occurs first, in order to review and discuss safety data, including adverse events, dose interruptions and dose modifications, as well as available pharmacokinetic data. At the

planned safety review meeting, Novartis and the investigators must reach a consensus based on the available safety and clinical pharmacology data, to decide whether to continue with enrolment on the study. In addition, the Novartis study team will perform regular data review on safety and efficacy data reported in the CRFs.

11 Data Collection and Database management

11.1 Data collection

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

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

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

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

In addition to data entered into the eCRF, requisition forms may also need to be completed for (e.g. PK, Biomarker etc.) sample collection.

11.2 Database management and quality control

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

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

Dates of screenings, enrolments, randomizations (if applicable), screen failures and study completion, as well as randomization codes (if applicable) and kit numbers and data about sabatolimab and azacitidine dispensed to the participant and all dose changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis at specific timelines.

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

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

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis/delegated Contract Research Organization (CRO) representative will review the protocol and data capture requirements (i.e., eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and Good Clinical Practice (GCP) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/delegated CRO/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters and provide reports to Novartis clinical teams to assist with trial oversight.

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

The first safety analysis (including adults from the first cohort) will be conducted when at least 6 evaluable participants have received sabatolimab in monotherapy at 400 mg dose level for at least 2 cycles of treatment. The second safety analysis (including adults from the second cohort) will be conducted when at least 9 evaluable participants have received sabatolimab in monotherapy at 800 mg dose level for at least 2 cycles of treatment.

The primary efficacy analysis will be conducted on all adult participants data (from both safety run-in, expansion monotherapy and combination cohorts) at the time all adult participants who are still receiving study treatment will have completed at least 6 cycles of treatment or will be followed for at least 6 months after the first dose of study treatment or will have discontinued from the study earlier.

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

All data will be summarized by dose cohort:

- Adults with sabatolimab 400 mg
- Adults with sabatolimab 800 mg
- Adults with azacitidine & sabatolimab combination
- Adolescents with sabatolimab monotherapy

For the combination cohort and the adolescent cohort, sabatolimab will be given at the recommended dose for expansion (see Section 6.5.2 for guidelines on determination of the recommended dose for expansion).

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

12.1 Analysis sets

The Full Analysis Set (FAS) comprises all participants that received any study treatment. Participants will be analyzed according to the treatment(s) received. A participant randomized in the combination cohort who receives only sabatolimab and no dose of azacitidine will be analyzed with participants randomized in the expansion monotherapy cohort (the treatment received).

The Safety Set includes all participants from the FAS.

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) between Cycle 1 Day 1 (first dose of sabatolimab) and the end of Cycle 2.

A participant has met the minimum exposure criterion if the participant takes 2 infusions of sabatolimab at full dose (400 mg or 800 mg) during the first 2 cycles of treatment.

Participants who do not experience a dose-limiting toxicity (DLT) during the first two cycles are considered to have sufficient safety evaluations if they have been observed for at least 28 days following the second dose of sabatolimab. Participants will be analyzed according to the study treatment received as defined for FAS.

12.2 Participant demographics and other baseline characteristics

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

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term.

12.3 Treatments

The duration of exposure to sabatolimab and azacitidine for the combination cohort only as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by descriptive statistics using the safety set.

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

The number of participants with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons will be summarized and all dosing data will be listed.

12.4 Analysis supporting primary objectives

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.

The primary efficacy objective is to assess the proportion of adult participants with AML and MRD+ post-aHSCT in FAS 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).

12.4.1 Definition of primary endpoint(s)

For the primary safety objectives (for adults and adolescents separately), the primary variable is the proportion of participants from the DDS who reported a dose-limiting toxicity (DLT) (see Section 6.5.3 for details) during the first two cycles.

For the primary efficacy objective, the primary variable is the proportion of adults from the FAS treated at the recommended dose for expansion (RDE) who report 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) as per investigator assessment (Table 8-3) after 6 cycles of study treatment.

12.4.2 Statistical model, hypothesis, and method of analysis

Primary safety analysis in adults (incidence of treatment-emergent dose-limiting toxicities including but not limited to GvHD)

Assessing whether sabatolimab at the tested dose levels does not lead to an unacceptable level of toxicity (DLTs) in adults will be guided by a Bayesian Logistic Regression Model (BLRM). This single-agent model will assess the relationship between the log-dose of sabatolimab and

the incidence of dose-limiting toxicities (DLTs). Details about this model is provided in Section 16.6.

The posterior probability that the true incidence of dose-limiting toxicity (DLT) including aGvHD and cGvHD is lower than 50% will be summarized after each cohort in the safety run-in part. If this posterior probability is less than 25%, it would be recommended to start the next cohort.

Primary safety analysis in adolescents (incidence of treatment-emergent dose-limiting toxicities including but not limited to GvHD)

Assessing whether sabatolimab at the recommended dose for adults does not lead to an unacceptable level of toxicity (DLTs) in adolescents will be guided by the same Bayesian Logistic Regression Model (BLRM) than used for the adult cohorts of the safety run-in part. Details about this model is provided in Section 16.6.

The posterior probability that the true incidence of dose-limiting toxicity (DLT) is lower than 50% will be summarized for the adolescent cohort.

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

A Bayesian design will be used to estimate the true rate of participants with no evidence of hematologic relapse after 6 cycles of study treatment 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. This Bayesian dual-criterion design will allow to base the trial success not only on the statistical significance for superiority against a certain threshold but also by considering a minimum clinically estimated effect size. The statistical significance threshold considered for trial success is a proportion of adult participants who remain with no evidence of hematologic relapse $\geq 15\%$ and 30% for sabatolimab in monotherapy and sabatolimab in combination with azacitidine, respectively. The clinically meaningful threshold considered for trial success is a proportion of adult participants who remain with no evidence of hematologic relapse $\geq 30\%$ and 50% for sabatolimab in monotherapy and sabatolimab in combination with azacitidine, respectively.

Trial success will be declared if at least one of the two study treatment (sabatolimab in monotherapy or sabatolimab in combination with azacitidine) is meeting both statistical and clinical criteria.

The decision criteria for adult participants treated with sabatolimab in monotherapy are the following:

- 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)
- 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 adult participants treated with sabatolimab in combination with azacitidine are the following:

- 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 ≥ 30% is at least 97.5% (statistical significance at 2.5% level, 1-sided)
- 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 ≥ 50%

Inferential summaries (e.g., mean, median, standard deviation, 95% credible intervals, and interval probabilities) 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 be also 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, as well as the 1-sided p-value will be provided by treatment arm (sabatolimab monotherapy and sabatolimab in combination with azacitidine). No adjustment of the type I error for multiplicity is planned for this study.

12.4.3 Handling of intercurrent events of primary estimand

Handling of remaining intercurrent events of the primary efficacy and safety estimands are described in Section 2.1.

12.4.4 Handling of missing values not related to intercurrent event

For the determination of the absence of evidence of hematologic relapse (ie, no evidence of bone marrow blasts ≥5%; no evidence of reappearance of blasts in the blood; no evidence of development of extramedullary disease) after 6 cycles of treatment, only the response assessment performed at Cycle 7 Day 1 or the response assessment performed 6 months after starting the study treatment is considered.

An adequate response assessment is considered any disease assessment indicating response status apart from “unknown” or “not done”. Evaluation of response relies on bone marrow, peripheral blood, and extramedullary disease assessment. In case of missing data for the full assessment required to qualify for a given response or in case of a more than 7 days difference between bone marrow aspirate/biopsy assessments and hematology assessments of the same visit, the overall assessment “unknown” was assigned unless relapse was seen in at least one compartment (i.e. bone marrow or blood).

A participant will be considered with no evidence of hematologic relapse if an adequate response assessment indicates a complete remission (CR) or a complete remission with incomplete hematologic recovery (CRi) response; and even if one or several inadequate response assessments ("unknown" or "not done") have been documented prior to the current adequate response assessment.

12.4.5 Sensitivity analyses

No sensitivity analyses are planned.

12.4.6 Supplementary analysis

A supplementary clinical question of interest is: how similar is the effect of sabatolimab, as monotherapy and in combination with azacitidine, on prevention of hematologic relapse (i.e., maintenance of CR or CRi) when the AML high risk population is defined based on the biomarker central review? In this supplementary estimand, all except the definition of the population will be the same as the primary estimand (Section 2.1).

The population considered for this supplementary estimand is all adult participants with AML who are in complete remission after having received an aHSCT and at high risk of relapse defined as positive MRD at baseline (determined by central assessment) any time at ≥ Day 60 after aHSCT and who have been tapered off immunosuppressive therapy.

12.4.7 Supportive analyses

A supportive clinical question of interest is: how similar is the effect of sabatolimab between the two doses tested (400 mg and 800 mg Q4W) on prevention of hematologic relapse (i.e., maintenance of CR or CRi) in participants with AML at high risk of relapse (MRD positivity)? In this supportive analysis, the proportion of participants with no evidence of hematologic relapse after 6 cycles of treatment with the exact 95% confidence interval will be presented for participants assigned to the sabatolimab dose level tested during the safety run-in part but not selected for the expansion part.

12.5 Analysis supporting secondary objectives

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

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, and (ii) the date when a new anti-neoplastic therapy or a donor leucocytes infusion (DLI) is started. 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 (Section 2.1).

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.

MRD conversion rate based on central MRD assessment

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.

GvHD-free/relapse-free survival (GRFS)

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, and (ii) the date when a new anti-neoplastic therapy or a donor leucocytes infusion (DLI) is started. 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.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by dose cohort.

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

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

1. Pre-treatment period: from day of participant's informed consent to the day before first dose of study treatment
2. On-treatment period: from day of first dose of study treatment to 30 days after last dose of study treatment
3. Post-treatment period: starting at day 31 after last dose of study treatment.

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

Adverse events

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period. The number (and percentage) of participants with treatment emergent adverse events will be summarized by primary system organ class, preferred term and maximum severity.

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

Separate summaries will be provided for:

- treatment emergent grade III or grade IV acute GvHD
- treatment emergent moderate to severe chronic GvHD
- treatment-emergent ≥ grade 3 immune-related adverse events not attributed to GvHD

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

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

Vital signs

All vital signs abnormalities will be summarized by visit.

Clinical laboratory evaluations

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

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

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

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

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

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

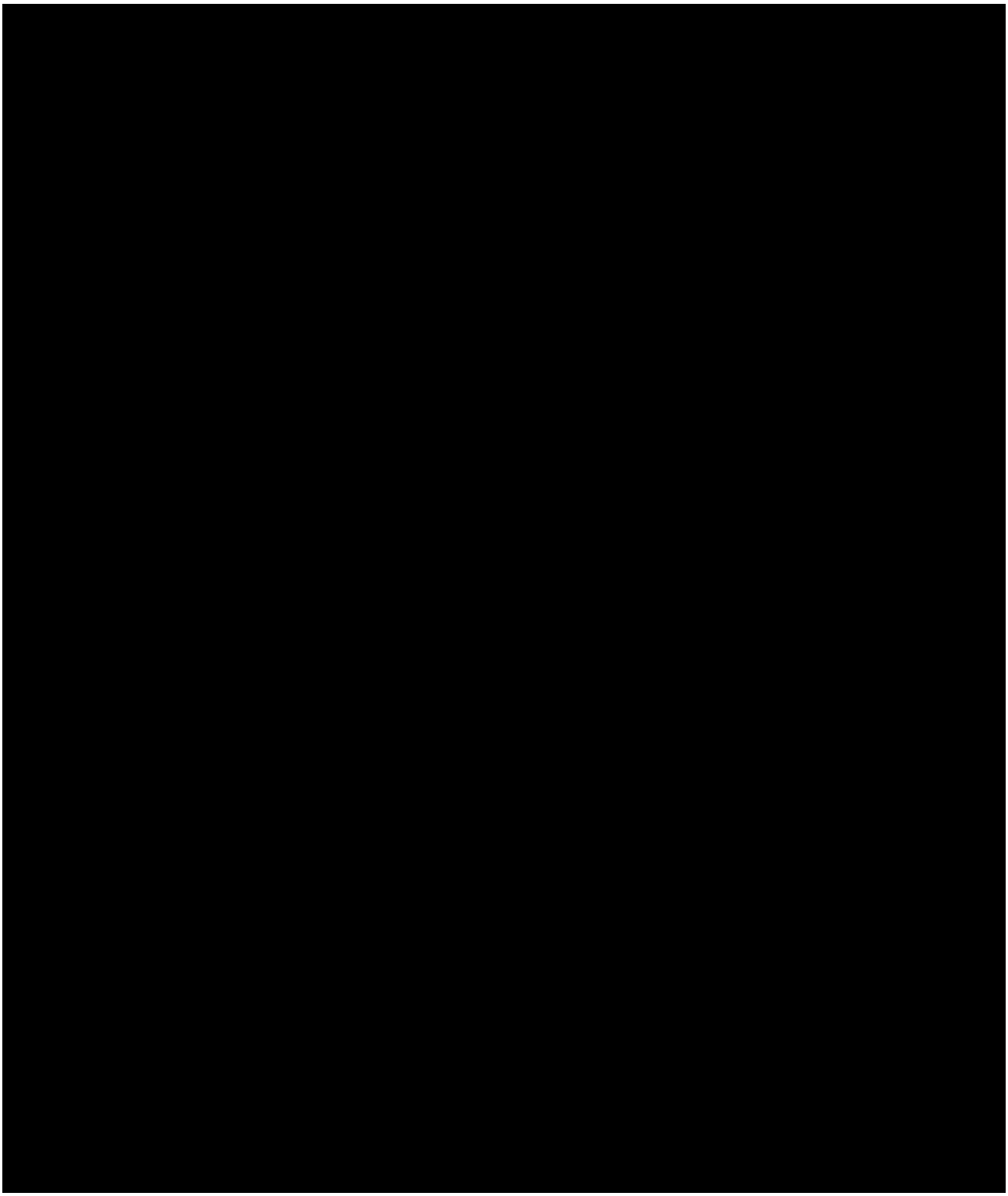
- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value

12.5.3 Pharmacokinetics

Sabatolimab plasma concentration data will be listed by participant and visit/sampling time point. Descriptive summary statistics will be provided by visit/sampling time point, including 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%. The minimum observed plasma or serum drug concentration (Cmin or Ctrough) at steady-state will be estimated and reported. Missing values for any PK parameters or concentrations will not be imputed and will be treated

as missing. The concentrations collected on Cycle 3 and later cycles are considered steady-state concentrations for sabatolimab.

All concentration data for sabatolimab versus time profiles will be displayed graphically.



[redacted]

12.7 Interim analyses

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). Decisions will be guided by a Bayesian analysis and the review of all relevant data available from all dose levels evaluated in the ongoing study including safety information, incidence and severity of aGvHD and cGvHD, incidence of DLTs, all CTCAE Grade ≥ 2 toxicity data, PK, and PD data from evaluable participants (Section 6.5.2). Such safety analyses

do not inflate the type I error for the primary efficacy hypothesis testing and thus no adjustment for multiplicity is required.

The primary analysis will be performed after all participants have completed at least 6 cycles of treatment or will be followed for at least 6 months after the first dose of study treatment or will have discontinued from the study earlier. A final analysis will be performed after all participants have completed the study (or discontinued earlier). Formal testing of the primary endpoint with full level alpha will be performed at the primary analysis time point.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

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.

Table 12-1 presents different scenarios for the incidence of DLTs in the two cohorts of the safety run-in part and the decision made based on the Bayesian logistic regression model using 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).

The 15% DLT rate corresponds to the anticipated intrinsic risk of GvHD in this post-transplant setting. Of note, no historical data has been considered in the Bayesian model as no participant was already treated with sabatolimab in this post-transplant setting.

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, we will select 50% as the threshold to qualify for an acceptable toxicity (i.e. probability to observe a DLT rate exceeding 50% is below 25%).

Table 12-1 Probability of unacceptable toxicity for different hypothetical scenarios

Number of participants with at least one DLT (including GvHD) among evaluable participants		**Probability to observe a DLT rate with three different definition of over-toxicity (>40%, >45% or >50%)**					
		DLT rate >40%		DLT rate >45%		DLT rate >50%	
1st cohort 400 mg	2nd cohort 800 mg	Next dose*	P(excessive toxicity)	Next dose*	P(excessive toxicity)	Next dose*	P(excessive toxicity)

Number of participants with at least one DLT (including GvHD) among evaluable participants		Probability to observe a DLT rate with three different definition of over-toxicity (>40%, >45% or >50%)					
1/6	--	800	0.219	800	0.166	800	0.125
2/6	--	400	0.211	400	0.145	400	0.094
3/6	--	Stop		stop		stop	
2/8	--	400	0.094	400	0.055	800	0.216
3/8	--	stop		400	0.199	400	0.129
0/6	2/9	800	0.038	800	0.016	800	0.007
0/6	3/9	800	0.136	800	0.076	800	0.040
0/6	4/9	400	0.012	800	0.214	800	0.134
0/6	5/9	400	0.025	400	0.012	400	0.005
1/6	3/9	800	0.212	800	0.125	800	0.068
1/6	4/9	400	0.068	400	0.033	800	0.184
1/6	5/9	400	0.130	400	0.072	400	0.036
2/8	3/9	400	0.052	800	0.179	800	0.097
2/8	4/9	400	0.106	400	0.053	800	0.224
* Next dose is the dose recommended by the BLRM for the next cohort or the expansion part of the study that satisfies the definition of an acceptable level of toxicity (probability of excessive toxicity (i.e. DLT rate ≥ 40, 45 or 50%) is less than 0.25.							

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 (ie, maintenance of CR or CRi), defined as absence of bone marrow blasts ≥5%; absence of reappearance of blasts in the blood; and absence of 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 12.4.2.

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 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 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) (Table 12-2). In the absence of historical data in participants treated with sabatolimab in this post-transplant setting, a uniform Beta (1,1) prior has been used for these sample size calculations.

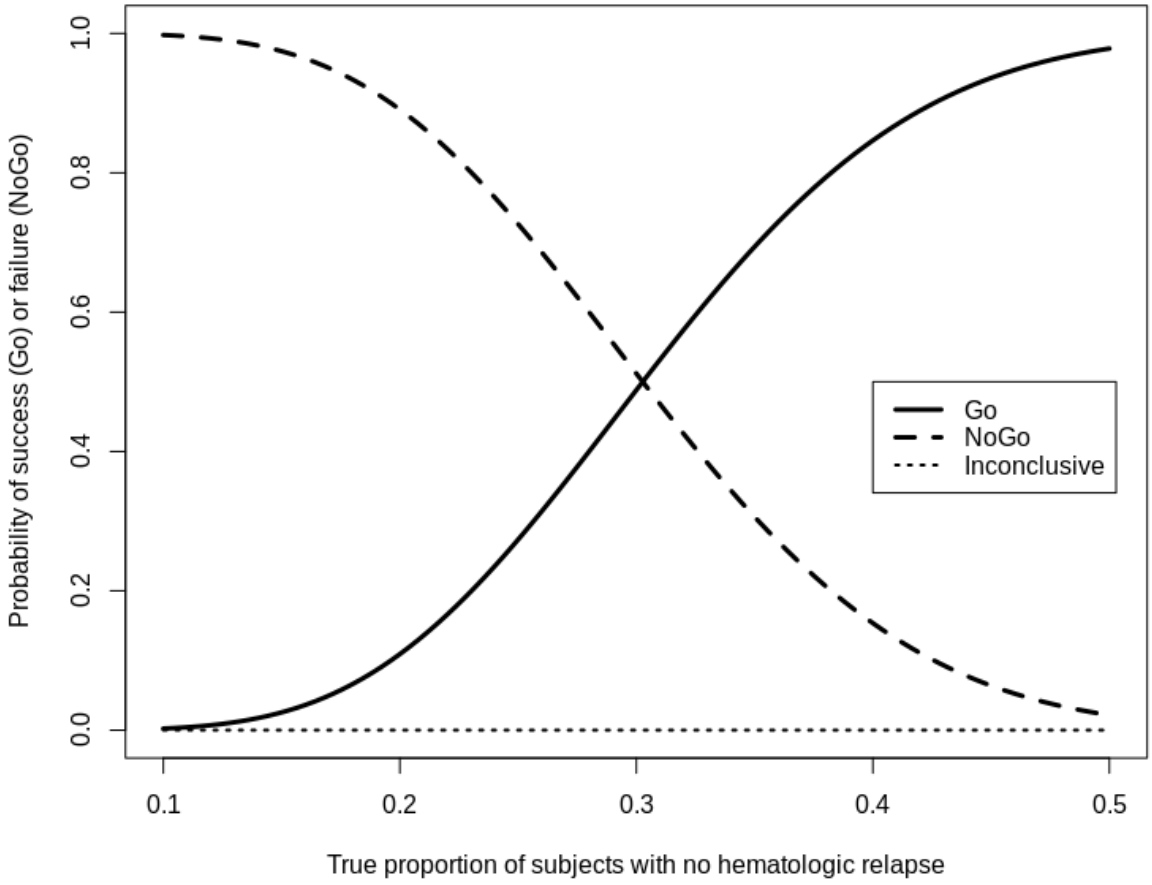
Operating characteristics for various true proportion of participants with no evidence of hematologic relapse in participants treated with sabatolimab in monotherapy are presented in

Figure 12-1. The type-I error under the null value (proportion of participants who remain with no evidence of hematologic relapse = 15%) is 2.5% and power is 69.4% and 84.6% assuming a true proportion of participants with no evidence of hematologic relapse of 35% and 40%, respectively.

Table 12-2 Data scenarios, inferential results and decisions for different values of the proportion of participants with no hematologic relapse in the sabatolimab monotherapy arm (n=25)

True proportion of participants with no hematologic relapse	Posterior median	Posterior probability for a positive effect (proportion of participants with no hematologic relapse ≥15%)	Decision for trial success
5/25 (20%)	21.5%	0.815	Failed
6/25 (24%)	25.3%	0.917	Failed
7/25 (28%)	29.1%	0.968	Failed
8/25 (32%)	32.9%	0.989	Successful
9/25 (36%)	36.7%	0.997	Successful
10/25 (40%)	40.5%	0.999	Successful

Figure 12-1 Operating characteristics for the proportion of participants with no hematologic relapse in the sabatolimab monotherapy arm



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) (Table 12-3). In the absence of historical data in participants treated with sabatolimab in this post-transplant setting, a uniform Beta (1,1) prior has been used for these sample size calculations.

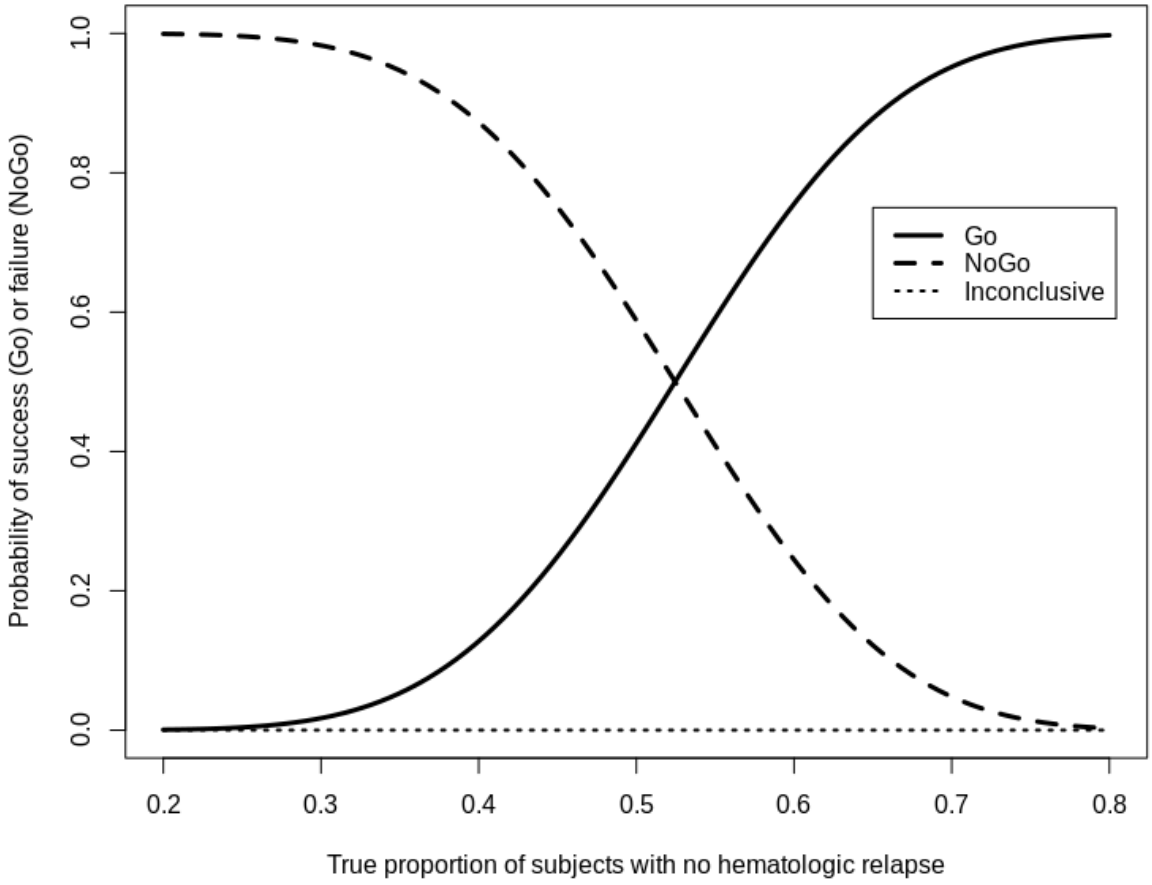
Operating characteristic for various true proportion of participants with no evidence of hematologic relapse after being treated with sabatolimab in combination with azacitidine are presented in Figure 12-2. The type-I error under the null value (proportion of participants with

no evidence of hematologic relapse = 30%) is 1.7% and power is 75.5% assuming a true proportion of participants with no evidence of hematologic relapse of 60%.

Table 12-3 Data scenarios, inferential results, and decisions for different values of the proportion of participants with no hematologic relapse in the combination arm (sabatolimab + azacitidine) (n=20)

True the proportion of participants with no hematologic relapse	Posterior median	Posterior probability for a positive effect (proportion of participants with no hematologic relapse ≥30%)	Decision for trial success
8/20 (40%)	40.6%	0.852	Failed
9/20 (45%)	45.3%	0.932	Failed
10/20 (50%)	50.0%	0.974	Failed
11/20 (55%)	54.7%	0.991	Successful
12/20 (60%)	59.4%	0.998	Successful
13/20 (65%)	64.1%	0.999	Successful

Figure 12-2 Operating characteristics for the proportion of participants with no hematologic relapse in the combination arm (sabatolimab + azacitidine)



These calculations were made using the software R (version 3.6.1) using the RBesT package.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

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

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

13.4 Quality Control and Quality Assurance

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

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

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

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case-by-case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to

Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

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

14.1 Protocol amendments

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

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

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

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16 Appendices

16.1 Appendix 1: Acute GvHD Staging Criteria (Harris et al 2016)

Organ staging will be performed according to updated NIH criteria as described by Harris et al (Harris et al 2016) in Table 16-1.

Table 16-1 Acute GvHD Staging Criteria (Harris et al 2016)

Stage	Skin (Active Erythema Only)	Liver (Bilirubin)	Upper GI	Lower GI (stool output/day)
Stage 0	No active (erythematous) GvHD rash	< 2 mg/dL	No or intermittent nausea, vomiting, or anorexia	Adult: <500mL/day or <3 episodes/day Child: <10mL/kg/day or <4 episodes/day
Stage 1	Maculopapular rash < 25% BSA	2-3 mg/dL	Persistent nausea, vomiting, or anorexia	Adult: 500-999mL/day or 3-4 episodes/day Child: 10-19.9mL/kg/day or 4-6 episodes/day
Stage 2	Maculopapular rash < 25% - 50% BSA	3.1-6 mg/dL		Adult: 1000-1500mL/day or 5-7 episodes/day Child: 20-30mL/kg/day or 7-10 episodes/day
Stage 3	Maculopapular rash > 50% BSA	6.1-15 mg/dL		Adult: >1500mL/day or > 7 episodes/day Child: >30mL/kg/day or > 10 episodes/day
Stage 4	Generalized erythrodema (>50% BSA) plus bullous formation and desquamation >5% BSA	> 15 mg/dL		Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume)
Overall clinical grade (based on most severe target organ involvement): Grade 0: No stage 1-4 of any organ. Grade I: Stage 1-2 skin without liver, upper GI or lower GI involvement. Grade II: Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI. Grade III: Stage 2-3 liver and/or stage 2-3 lower GI with stage 0-3 skin and/or stage 0-1 upper GI.				

Stage	Skin (Active Erythema Only)	Liver (Bilirubin)	Upper GI	Lower GI (stool output/day)
Grade IV: Stage 4 skin, liver or lower GI involvement, with stage 0-1 upper GI.				

16.2 Appendix 2: Grading of Chronic GvHD (NIH Consensus Criteria)

Grading of chronic GvHD as described by Jagasia et al (Jagasia et al 2015) should be performed as described below.

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† **SCORE % BSA** ☐ *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash/erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like GVHD	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
Other skin GVHD features (NOT scored by BSA) **Check all that apply:** ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Poikiloderma ☐ Severe or generalized pruritus ☐ Hair involvement ☐ Nail involvement ☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
MOUTH *Lichen planus-like features present:* ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

Organ scoring of chronic GvHD. ECOG indicates Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status; LPS, Lansky Performance Status; BSA, body surface area; ADL, activities of daily living; LFTs, liver function tests; AP, alkaline phosphatase; ALT, alanine aminotransferase; ULN, normal upper limit. *Weight loss within 3 months. Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired

mobility or ulceration (Score 3), the higher level should be used for the final skin scoring. To be completed by specialist or trained medical providers. **Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* ☐ **Yes** ☐ **No** ☐ **Not examined**	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GI Tract ***Check all that apply:*** ☐ Esophageal web/ proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss ≥5%* ☐ Failure to thrive	☐ No symptoms	☐ Symptoms without significant weight loss* (<5%)	☐ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____				
LIVER	☐ Normal total bilirubin and ALT or AP < 3 x ULN	☐ Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	☐ Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	☐ Elevated total bilirubin > 3 mg/dL
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LUNGS** **Symptom score**:	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
Lung score: % FEV1 ☐	☐ FEV1≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%
Pulmonary function tests ☐ Not performed				
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GENITAL TRACT (*See Supplemental figure*‡) ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs‡ and females with or without discomfort on exam	☐ Moderate signs‡ and may have symptoms with discomfort on exam	☐ Severe signs‡ with or without symptoms
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

☐ Ascites (serositis)___	☐ Myasthenia Gravis___	
☐ Pericardial Effusion___	☐ Peripheral Neuropathy___	☐ Eosinophilia > 500/µl___
☐ Pleural Effusion(s)___	☐ Polymyositis___	☐ Platelets <100,000/µl ___
☐ Nephrotic syndrome___	☐ Weight loss>5%* without GI symptoms___	☐ Others (specify):

Overall GVHD Severity *(Opinion of the evaluator)* ☐ **No GVHD** ☐ **Mild** ☐ **Moderate** ☐ **Severe**

Photographic Range of Motion (P-ROM)

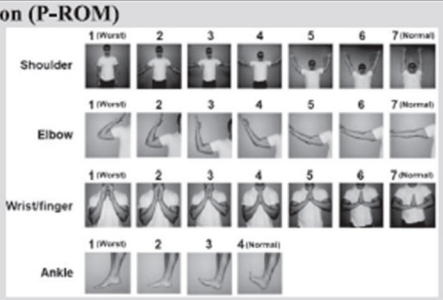

Table 16-2 NIH global severity of chronic GvHD

Mild	1 or 2 organs involved with no more than score 1 plus Lung score 0 • Mild oral symptoms, no decrease in oral intake • Mild dry eyes, lubricant eyedrops ≤3x/day
Moderate	3 or more organs involved with no more than score 1 OR Lung score 1 (FEV1 60-79% or dyspnea with stairs) OR

	At least 1 organ (not lung) or site with score 2 • 19-50% body surface area involved or superficial sclerosis • Moderate dry eyes, eyedrops≥3x/days or punctal plugs
Severe	At least 1 organ or site with score 3 • ≥ 50% body surface area involved • Deep sclerosis, impaired mobility or ulceration • Severe oral symptoms with major limitation in oral intake • Severe dry eyes affecting ADL OR Lung score 2 or 3(FEV1 40-59% or dyspnea walking on flat ground)

(Jagasia et al 2015, Lee 2017)

Key points: In skin: higher of the 2 scores to be used for calculating global severity. If the entire abnormality in an organ is noted to be unequivocally explained by a non-GvHD documented cause, that organ is not included for calculation of the global severity. If the abnormality in an organ is attributed to multifactorial causes (GvHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

16.3 Appendix 3: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-3 Specific Renal Alert Criteria and Actions

Renal Event	Actions
Confirmed serum creatinine increase 25 – 49%	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase 50 % [+]**OR if <18 years old, eGFR 35 mL/min/1.73 m^2**	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider patient hospitalization and specialized treatment
New onset dipstick proteinuria ≥ 3+ OR Protein-creatinine **ratio** ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)	• Consider causes and possible interventions • Assess serum albumin & serum total protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria ≥ 3+ on urine dipstick	• Assess & document • Repeat assessment to confirm • Distinguish hemoglobinuria from hematuria • Urine sediment microscopy • Assess sCr • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

[+] Corresponds to Kidney Disease Improving Global Outcomes (KDIGO) criteria for Acute Kidney Injury

Additional specialized assessments are available to assess renal function or renal pathology. (Note: In exceptional cases, when a nephrologist considers a renal biopsy, it is recommended to make slide specimen available for evaluation by the RSG to potentially identify project-wide patterns of nephrotoxicity.)

Whenever a renal event is identified, a detailed patient history and examination are indicated to identify and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5-minute rest, with an appropriate cuff size)
- Signs and symptoms like fever, headache, shortness of breath, back or abdominal pain, dysuria or hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output

- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other diseases or causes, e.g., dehydration due to delirium, tumor lysis

Table 16-4 Renal Event Follow Up

FOLLOW-UP OF RENAL EVENTS
Assess, document and record in CRF: • Urine dipstick and sediment microscopy evidence of DIN: crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells • Blood pressure and body weight • Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output
Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the CRF
Monitor patient regularly (frequency at investigator's discretion) until: • Event resolution: (sCr within 10% of baseline or protein-creatinine ratio< 1 g/g Cr, or ACR <300 mg/g Cr) or • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months. • Analysis of urine markers in samples collected over the course of the DIN event

16.4 Appendix 4: Infection Severity Grading

Infections will be categorized according to type (i.e. bacterial, viral and fungal) and Blood and Marrow Transplant Clinical Trials Network (BMT CTN) severity (i.e. grade III infection, yes vs. no) (BMT CTN 2013).

Table 16-5 Severity grading table and recurrence interval definitions

Type of Infection/Severity Grade	Grade 1	Grade 2	Grade 3
Bacterial infections	Bacterial focus NOS requiring no more than 14 days of therapy for treatment (e.g. urinary tract infection)	Bacteremia (except CoNS) without severe sepsis***	Bacteremia with deep organ involvement (e.g. with new or worsening pulmonary infiltrates; endocarditis)
	Coag Neg Staph (S. epi), Corynebacterium, or Proprioniobacterium bacteremia	Bacterial focus with persistent signs, symptoms or persistent positive cultures requiring greater than 14 days of therapy	Severe sepsis with bacteremia
	Cellulitis responding to initial therapy within 14 days	Cellulitis requiring a change in therapy d/t progression	Fasciitis requiring debridement
		Localized or diffuse infections requiring incision with or without drain placement	
		Any pneumonia documented or presumed to be bacterial	Pneumonia requiring intubation
			Brain abscess or meningitis without bacteremia
	C. Difficile toxin positive stool with diarrhea < 1L without abdominal pain (child < 20 mL/kg)	C. Difficile toxin positive stool with diarrhea > 1L (child > 20 mL/kg) or with abdominal pain	C. Difficile toxin positive stool with toxic dilatation or renal insufficiency with/without diarrhea
Fungal infections	Superficial candida infection (e.g. oral thrush, vaginal candidiasis)	Candida esophagitis (biopsy proven)	Fungemia including Candidemia

Type of Infection/Severity Grade	Grade 1	Grade 2	Grade 3
		Proven or probable fungal sinusitis confirmed radiologically without orbital, brain, or bone involvement	Proven or probable invasive fungal infections (e.g. Aspergillus, Mucor, Fusarium, Scedosporium)
			Disseminated infections (defined as multifocal pneumonia, presence of urinary or blood antigen, and/or CNS involvement) with Histoplasmosis, Blastomycosis, Coccidiomycosis, or Cryptococcus
			Pneumocystis jiroveci pneumonia (regardless of PaO2 level)
Viral infections	Mucous HSV infection		
	Dermatomal Zoster	VZV infection with 3 or more dermatomes	Severe ZVZ infection (coagulopathy or organ involvement)
	Asymptomatic CMV viremia untreated or a CMV viremia with viral load decline by at least 2/3 of the baseline value after 2 weeks of therapy	Clinically active CMV infection (e.g. symptoms, cytopenias) or CMV viremia not decreasing by at least 2/3 of the baseline value after 2 weeks of therapy	CMV end-organ involvement (pneumonitis, enteritis, retinitis)
	EBV reactivation not treated with rituximab	EBV reactivation requiring institution of therapy with rituximab	EBV PTLD
	Adenoviral conjunctivitis asymptomatic viruria, asymptomatic stool shedding and viremia not requiring treatment	Adenoviral upper respiratory infection, viremia, or symptomatic viruria requiring treatment	Adenovirus with end-organ involvement (except conjunctivitis and upper respiratory tract)
	Asymptomatic HHV-6 viremia untreated or an HHV-6 viremia with a viral load decline by at least 0.5 log after 2 weeks of therapy	Clinically active HHV-6 infection (e.g. symptoms, cytopenias) or HHV-6 viremia without viral load decline 0.5 log after 2 weeks of therapy	

Type of Infection/Severity Grade	Grade 1	Grade 2	Grade 3
	BK viremia or viruria with cystitis not requiring intervention	BK viremia or viruria with clinical consequence requiring prolonged therapy and/or surgical intervention	
		Enterocolitis with enteric viruses	
		Symptomatic upper tract respiratory virus	Lower tract respiratory viruses
	Viremia (virus not otherwise specified) not requiring therapy	Any viremia (virus not otherwise specified) requiring therapy	
			Any viral encephalitis or meningitis
Parasitic infections			CNS or other organ toxoplasmosis
			Strongyloides hyperinfection
Non-microbiologically defined infections	Uncomplicated fever with negative cultures responding within 14 days		
	Clinically documented infection not requiring inpatient management	Pneumonia or bronchopneumonia not requiring mechanical ventilation	Any acute pneumonia requiring mechanical ventilation
		Typhlitis	
			Severe sepsis*** without an identified organism

*Concomitant or multi-microbial infections are graded according to the grade of the infection with the higher grade of severity

**Therapy includes both PO and IV formulations

***Severe sepsis:

Adults:

Hypotension

- A systolic blood pressure of <90 mm hg or a reduction of >40 mm hg from baseline in the absence of other causes for hypotension

Multiple Organ Dysfunction Syndrome

- 2 or more of the following: Renal failure requiring dialysis, respiratory failure requiring bipap or intubation, heart failure requiring pressors, liver failure

Pediatrics:

- Pediatric SIRS definition and suspected or proven infection and cardiovascular dysfunction or ARDS or TWO or MORE other organ dysfunctions

Pediatric SIRS definition:

Two or more of the following, one of which must be abnormal temperature or leukocyte count

1. Core temperature >38.5C or < 36C
2. Tachycardia, otherwise unexplained persistent in absence of external stimulus, chronic drugs or painful stimuli. or bradycardia, in < 1 year old, otherwise unexplained persistent.
3. Tachypnea or mechanical ventilation for an acute process not related to underlying neuromuscular disease or general anesthesia
4. Leukocytosis or leukopenia for age (not secondary to chemotherapy) or >10% bands

Pediatric organ dysfunction criteria:

Cardiovascular: despite administration of fluid bolus >40 ml/kg in 1 hour:

- Hypotension <5th percentile for age (or per Table 16-3)
- Pressors at any dose
- Two of the following:
  - Capillary refill > 5 secs
  - Core to peripheral temperature gap > 3oC
  - Urine output < 0.5 mL/kg/hr
  - Unexplained metabolic acidosis (Base deficit > 5.0 mEq/L)
  - Blood lactate > 2 x ULN

Respiratory:

- ARDS or
- Intubated or
- >50% FiO2 to maintain SaO2 > 92%

Neurological:

- Glasgow Coma Score ≤ 11 or
- Acute change in mental status with a decrease in GSC ≥3 pts from abnormal baseline

Renal:

- Serum creatinine ≥ 2 x ULN for age or 2-fold increase in baseline creatinine

Hepatic:

- Total bilirubin ≥ 4 mg/dL or
- ALT ≥2 x ULN for age

Table 16-6 Four age groups relevant to HCT

Age	Tachycardia (bpm)	Bradycardia (bpm)	Tachypnea (breaths/min)	Leukocytosis / Leukopenia (WBC)	Hypotension Systolic BP (mmHg)
1 mo to 1 yr	>180	<90	>34	>17.5 to <5.0	<100

Age	Tachycardia (bpm)	Bradycardia (bpm)	Tachypnea (breaths/min)	Leukocytosis / Leukopenia (WBC)	Hypotension Systolic BP (mmHg)
2 yr to 5 yr	>140	NA	>22	>15.5 to <6.0	<94
6 yr to 12 yr	>130	NA	>18	>13.5 to <4.5	<105
13 yr to < 18 yr	>110	NA	>14	>11 to <4.5	<117

Disseminated Infections:

1. Two or more non-contiguous sites with the SAME organism
2. A disseminated infection can occur at any level of severity, but most will be grade 2 or 3.

Recurrence Intervals to Determine Whether an Infection is the Same or New:

1. CMV, HSV, EBV, HHV6: 2 months (< 60 days)
2. VZV, HZV: 2 weeks (< 14 days)
3. Bacterial, non-C. difficile: 1 week (< 7 days)
4. Bacterial, C. difficile: 1 month (< 30 days)
5. Yeast: 2 weeks (< 14 days)
6. Molds: 3 months (< 90 days)
7. Helicobacter: 1 year (< 365 days)
8. Adenovirus, Enterovirus, Influenza, RSV, Parainfluenza, Rhinovirus: 2 weeks (< 14 days)
9. Polyomavirus (BK virus): 2 months (< 60 days)

For infections coded as “Disseminated” per the Infection Form, any previous infection with the same organism but different site within the recurrence interval for that organism will be counted as part of the disseminated infection.

16.5 Appendix 5: Patient Past History and Disease Characteristics

AML diagnosis: diagnosis of AML will be reported as defined by the 2016 World Health Organization (WHO) AML classification (Arber et al 2016).

Table 16-7 2016 WHO AML classification

1	AML with recurrent genetic abnormalities	• AML with t(8;21)(q22;q22), RUNX1-RUNX1T1. • AML with inv(16)(p13.1;q22) or t(16;16)(p13.1;q22), CBFB-MYH11. • Acute promyelocytic leukemia (APL) with PML-RARA. • AML with t(9;11)(p21.3;q23.3), MLLT3-KMT2A. • AML with t(6;9)(p23;q34.1), DEK-NUP214. • AML with inv(3)(q21.3;q26.2) or t(3;3)(q21.3;q26.2), GATA2, MECOM. • AML (megakaryoblastic) with t(1;22)(p13.3;q13.3), RBM15-MKL1. • AML with BCR-ABL1 (provisional entity). • AML with mutated NPM1. • AML with biallelic mutations of CEBPA. • AML with mutated RUNX1 (provisional entity).
2	AML with myelodysplasia-related features	
3	Therapy-related myeloid neoplasms	
4	AML, Not Otherwise Specified (NOS)	• AML with minimal differentiation (FAB classification M0). • AML without maturation (FAB classification M1). • AML with maturation (FAB classification M2). • Acute myelomonocytic leukemia (FAB classification M4). • Acute monoblastic/monocytic leukemia (FAB classification M5a and M5b). • Pure erythroid leukemia (FAB classification M6a and M6b). • Acute megakaryoblastic leukemia (FAB classification M7). • Acute basophilic leukemia. • Acute panmyelosis with myelofibrosis.
5	Myeloid sarcoma	
6	Myeloid proliferations related to Down syndrome:	• Transient abnormal myelopoiesis (TAM). • Myeloid leukemia associated with Down syndrome.
7	Acute Leukemias of Ambiguous Lineage	• Acute undifferentiated leukemia. • Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); BCR-ABL1. • MPAL with t(v;11q23.3); KMT2A rearranged. • MPAL, B/myeloid, NOS.

		• MPAL, T/myeloid, NOS.

Cytogenetics and risk stratification: cytogenetic risk category will be reported according to the 2017 European LeukemiaNet (ELN) recommendations (Döhner et al 2017).

Table 16-8 2017 ELN risk stratification by genetics

Risk category*	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); RUNX1-RUNX1T1 inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}† Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡ Cytogenetic abnormalities not classified as favorable or adverse

Adverse	t(6;9)(p23;q34.1); *DEK-NUP214*
	t(v;11q23.3); *KMT2A* rearranged
	t(9;22)(q34.1;q11.2); *BCR-ABL1*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* -5 or del(5q); -7; -17/abn(17p)
	Complex karyotype,§ monosomal karyotype‖
	Wild-type *NPM1* and *FLT3*-ITD^{high}†
	Mutated RUNX1{
	Mutated ASXL1{
	Mutated TP53#

Frequencies, response rates, and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific genetic lesions indicated.

*Prognostic impact of a marker is treatment-dependent and may change with new therapies.

†Low, low allelic ratio (,0.5); high, high allelic ratio ($0.5); semiquantitative assessment of *FLT3*-ITD allelic ratio (using DNA fragment analysis) is determined as ratio of the area under the curve "*FLT3*-ITD" divided by area under the curve "*FLT3*-wild type"; recent studies indicate that AML with *NPM1* mutation and *FLT3*-ITD low allelic ratio may also have a more favorable prognosis and participants should not routinely be assigned to allogeneic HCT.

‡The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.

§Three or more unrelated chromosome abnormalities in the absence of 1 of the WHO-designated recurring translocations or inversions, that is, t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR-ABL1*.

‖Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality (excluding core-binding factor AML).

{ These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.

#TP53 mutations are significantly associated with AML with complex and monosomal karyotype.

Molecular markers and risk stratification:

In addition to basic cytogenetic analysis, molecular markers that can help refining prognostics groups, particularly in participants with a normal karyotype, include: NPM1, FLT3 (FLT3-ITD and FLT3-TKD), CEBPA, isocitrate dehydrogenase 1 and 2 (IDH1/2), DNA methyltransferase 3A (DNMT3A), c-KIT, MLL, TP53, RUNX1, and ASXL1 gene mutations (National Comprehensive Cancer 2020).

16.6 Appendix 6: Statistical details on the Bayesian Logistic Regression Model (BLRM)

Statistical Models

The safety run-in part of this study to confirm that the sabatolimab is safe will be guided by a Bayesian analysis of dose limiting toxicity (DLT) data. The statistical model will be a Bayesian Logistic Regression Model (BLRM) consisting of a single agent dose-DLT component.

Let π (d) be the risk of DLT for sabatolimab given as a single agent Q4W at dose d. The single agent dose-DLT model is as follow:

$$\text{logit}(\pi(d))=\log(\alpha)+\beta \log(d/d^{*})$$

where d^{*}= 800 mg Q4W (reference dose of sabatolimab) is used to scale the doses of sabatolimab. Hence, α (>0) is the single-agent odd of a DLT at 800 mg Q4W; β (>0) is the increase in the log-odds of a DLT by a unit increase in log-dose.

Taking into account the intrinsic risk of GvHD (which is part of the DLT definition) in the post-transplant setting, we selected a weakly informative prior 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.

No meta-analytic-predictive (MAP) approach was used to derive the prior distribution as historical data are not available in this post-transplant setting.

The prior distribution is specified in Table 16-9.

Table 16-9 Prior distribution

Parameter	Prior distribution
μ1	N(mean = logit(0.15), sd = 2)
μ2	N(mean = 0, sd=1)

The recommended dose for expansion will be the highest dose between 400 mg and 800 mg Q4W for which the probability of excessive toxicity (i.e. DLT rate ≥ 50%) is less than 0.25.

The summary of prior distribution of DLT rates is specified in Table 16-10.

Table 16-10 Summary of prior distribution of DLT rates

Dose of sabatolimab	Prior probabilities that P(DLT) is in the interval:		Mean	SD	Quantiles		
	[0, 0.50)	[0.50,1]			2.5%	50%	97.5%
400 mg Q4W	0.897	0.103	0.163	0.220	0.000	0.061	0.813
800 mg Q4W	0.806	0.194	0.257	0.264	0.003	0.151	0.900

Hypothetical on-study scenarios

To illustrate the performance of the BLRM used to guide the tolerability assessment in the safety run-in part for sabatolimab in monotherapy, hypothetical data scenarios are displayed in Table 16-11. Decision will be based on additional safety, PK or PD information.

Table 16-11 Probability of unacceptable toxicity for different hypothetical scenarios

Number of participants with at least one DLT (including GvHD) among evaluable participants		**Probability to observe a DLT rate with three different definition of over-toxicity (>40%, >45% or >50%)**					
		DLT rate >40%		DLT rate >45%		DLT rate >50%	
1st cohort 400 mg	2nd cohort 800 mg	Next dose*	P(excessive toxicity)	Next dose*	P(excessive toxicity)	Next dose*	P(excessive toxicity)
1/6	--	800	0.219	800	0.166	800	0.125
2/6	--	400	0.211	400	0.145	400	0.094
3/6	--	stop		Stop		stop	
2/8	--	400	0.094	400	0.055	800	0.216
3/8	--	stop		400	0.199	400	0.129
0/6	2/9	800	0.038	800	0.016	800	0.007
0/6	3/9	800	0.136	800	0.076	800	0.040
0/6	4/9	400	0.012	800	0.214	800	0.134
0/6	5/9	400	0.025	400	0.012	400	0.005
1/6	3/9	800	0.212	800	0.125	800	0.068
1/6	4/9	400	0.068	400	0.033	800	0.184
1/6	5/9	400	0.130	400	0.072	400	0.036
2/8	3/9	400	0.052	800	0.179	800	0.097
2/8	4/9	400	0.106	400	0.053	800	0.224
* Next dose is the dose recommended by the BLRM for the next cohort or the expansion part of the study that satisfies the definition of an acceptable level of toxicity (probability of excessive toxicity (i.e. DLT rate ≥ 40, 45 or 50%) is less than 0.25.							

Operating characteristics

The following exact operating characteristics were performed for different true values of DLT rate observed in the safety run-in part (participants treated with sabatolimab in monotherapy at 400 or 800 mg Q4W). Based on simulations with a 50% threshold to qualify for an excessive toxicity: when the true DLT rate observed in participants treated with sabatolimab 400 mg and 800 mg is equal to 40% and 50% respectively, the probability to stop the trial is 0.38 and the probability to start the expansion part of the trial with sabatolimab at 400 mg and 800 mg is 0.50 and 0.13 respectively (Table 16-12).

Table 16-12 Operating characteristics for different true values of DLT rate

True DLT rates	Probability to declare an excessive toxicity for three different thresholds to qualify for an excessive toxicity

1st cohort	2nd cohort	DLT rate >40%			DLT rate >45%			DLT rate >50%		
400 mg	800 mg	400 mg	800 mg	both doses	400 mg	800 mg	both doses	400 mg	800 mg	both doses
15%	20%	0.248	0.683	0.049	0.244	0.709	0.047	0.170	0.806	0.024
20%	30%	0.413	0.427	0.160	0.386	0.502	0.112	0.306	0.615	0.079
30%	40%	0.472	0.163	0.365	0.504	0.213	0.283	0.477	0.318	0.205
40%	50%	0.372	0.053	0.575	0.448	0.079	0.473	0.496	0.127	0.377
Operating characteristics are performed with R3.6.1 with 1000 simulations and by considering a sample size of 6 to 8 participants for the first cohort and a sample size of 9 to 12 participants for the second cohort.										