NOVARTIS

Oncology Clinical Development

MBG453 (sabatolimab)

Oncology Clinical Trial Protocol CMBG453B1US01 / NCT04878432

Single-arm, open label, phase II study of MBG453 (sabatolimab) added to FDA approved Hypomethylating agents of investigator's choice (IV/SC/Oral) for patients with intermediate, high or very high risk myelodysplastic syndrome (MDS) as per IPSS-R criteria (US multi-center) (STIMULUS MDS-US)

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List of abbreviations

ADA	Anti-drug Antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	Acute myeloid leukemia
ANA	Antinuclear antibodies
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BLQ	Below the Limit of Quantitation
BMA	Bone marrow aspirate
BSA	Body surface area
BUN	blood urea nitrogen
CBC	Complete Blood Count
C1D1	Cycle 1 Day 1
CFR	Code of Federal Regulation
CMML	Chronic myelomonocytic leukemia
CR	Complete Remission
CRF	Case Report/Record Form (paper or electronic)
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DDI	Drug-Drug Interaction
DILI	Drug Induced Liver Injury
DNA	Deoxyribonucleic acid
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOT	End of treatment
ePRO	Electronic Patient Reported Outcome
[redacted]	[redacted]
ESA	Erythropoiesis Stimulating Agent
ESMO	European Society for Medical Oncology
[redacted]	[redacted]
FAS	Full Analysis Set
FDA	Food and Drug Administration

GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
GGT	Gamma-glutamyl-transferase
GLDH	Glutamate dehydrogenase
HAV	Hepatitis A virus
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HI	Hematologic improvement
Hgb	Hemoglobin
HI-E	Erythroid
HI-P	Platelet
HI-N	Neutrophil
HIV	human immunodeficiency virus
HMA	Hypomethylating agent
HSCT	Hematopoietic stem cell transplantation
IV	Intravenous
IA	Interim Analysis
ICF	informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
[redacted]	[redacted]
imAE	immune-mediated adverse event
INQOVI	Oral Decitabine
INR	International normalized ratio
IPSS-R	International Prognostic Scoring System
irAE	immune related adverse event
IRB	Institutional Review Board
IUD	Intrauterine Device
IUS	Intrauterine System
IWG	International Working Group
LC-MS	Liquid Chromatography Mass Spectrometry
LDH	lactate dehydrogenase
LFT	Liver function test
LMWH	Low Molecular Weight Heparin
LPLV	Last Patient Last Visit
mAB	Monoclonal antibody
MCH	mean cell hemoglobin

MCHC	mean corpuscular hemoglobin concentration
mCR	marrow Complete Remission
MCV	mean corpuscular volume
MDS	Myelodysplastic syndromes
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical dictionary for regulatory activities
Med Hx	Medical History
Mg	milligram(s)
mL	milliliter(s)
Ml	milliliter(s)
[redacted]	[redacted]
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
[redacted]	[redacted]
NK	Natural Killers
NR	not reached
ORR	Overall Response Rate
OS	Overall survival
[redacted]	[redacted]
PB	Peripheral Blood
PCR	Polymerase Chain Reaction
PD	pharmacodynamic(s)
PD-1	Programmed cell death protein 1
PFS	Progression free survival
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PK	pharmacokinetic(s)
PR	Partial remission
PRO	Patient Reported Outcome
PS	Performance status
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RBC	red blood cell(s)
RNA	Ribonucleic acid
PK	Pharmacokinetic(s)
PT	prothrombin time
QD	Once a day
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
[redacted]	[redacted]

R Value	ALT/ALP x ULN
RAP	The Report and Analysis Plan
RBC	red blood cell(s)
REB	Research Ethics Board
RU	Resource Utilization
SC	Subcutaneous
SAE	serious adverse event
SSC	Steering committee
SD	Stable disease
SOC	Standard of Care
sTIM-3	Soluble T-cell immunoglobulin domain and mucin domain-3
SUSAR	Suspected Unexpected Serious Adverse Reactions
T3	Triiodothyronine (thyroid hormone)
T4	Thyroxine (thyroid hormone)
TBL	total bilirubin
TIM-3	T-cell immunoglobulin domain and mucin domain-3
TLS	Tumor lysis syndrome
TSH	Thyroid-Stimulating Hormone
ULN	upper limit of normal
WBC	white blood cell(s)
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Combination drug	Any drug that is combined to a specified regimen
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)
Enrollment	Point/time of participant entry into the study and all screening procedures have been completed/ eligibility criteria met (C1D1)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up), which applies across all arms of a study.
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug” or “test substance”
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Participant	An individual who has consented to participate in this study. The term Participant may be used to describe either a healthy volunteer or a patient.
Participant number	A number assigned to each participant who enrolls in the study. When combined with the center number, a unique identifier is created for each participant in the study.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Screen Failure	A participant who is screened but is not treated or enrolled
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, completion of treatment, etc.
Study completion	Point/time at which the participant came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when participant permanently stops taking study drug for any reason; may or may not also be the point/time of premature participant withdrawal.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the participant permanently stops taking study treatment prior to the defined study treatment completion date

Amendment 2 (22-Dec-2022)

Amendment rationale

As of the release of this amendment, 39 subjects have been enrolled in this trial.

The purpose of this amendment is to clarify and provide an update on the development strategy of sabatolimab (MBG453). Novartis has decided to permanently halt recruitment in the ongoing CMBG453B1US01 (STIMULUS MDS-US) and STIMULUS MDS-3 trials based on a reevaluation of the development strategy for sabatolimab. Patients who are currently on study treatment or in follow-up may continue in both studies as per the respective protocol.

Novartis confirms the decision to halt recruitment is not based on any safety findings or safety concerns with sabatolimab, either in combination with a hypomethylating agent (HMA) or as part of a triplet combination with venetoclax and azacitidine. Novartis remains engaged in the development of sabatolimab and all other sabatolimab trials will continue as planned.

Recruitment was halted for the STIMULUS MDS-US study on 30-Sep-2022.

This protocol amendment will be shortening the timeline of the study as well as various administrative changes.

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.

- Glossary of terms: Definition for enrollment was clarified.
- Protocol summary : Timepoints for analysis and study periods were clarified. Data analysis and enrollment numbers were updated per adjustment.
- Section 2 : Timepoints for analysis was clarified.
- Section 3 : Timepoints and study periods were adjusted.
- Section 4.4 : Timepoints for reporting was clarified.
- Section 5 : Enrollment numbers were adjusted.
- Section 6.1 : Dosing administration guidelines were updated.
- Section 6.1.4 : Duration of study was adjusted.
- Table 8-1 : Duration of study and assessments were adjusted.
- Section 8.3 : Number of assessments was adjusted.
- Table 8-7 : Number of assessments was adjusted.
- Talbe 8-8 : Number of assessments was adjusted.
- Section 12.8 : Enrollment numbers were adjusted.

IRBs/IECs

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

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

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

Amendment 1 (01-Apr-2021)

Amendment rationale

As of the release of this amendment, 0 subjects have been enrolled in this trial.

The purpose of this amendment is to clarify, in particular, the inclusion criteria related to the eligibility for intensive chemotherapy and stem cell transplantation, as well as the exclusion criteria related to cardiac abnormalities. Additionally, as new treatment options may be available for patients with AML, study treatment beyond progression in case of acute leukemia (per WHO 2016, as defined as ≥20% blasts in bone marrow and/or peripheral blood) is not permitted any longer. Definitions of the RBC or platelet transfusion dependence and transfusion independence in Table 8-2 were updated. The same pre-specified period of observation (i.e., 8 weeks) will be used to determine the transfusion status throughout the study. The interval of 8 weeks is selected, as it is in line with the assessment of transfusions for hematologic improvement and is acceptable to evaluate the transfusion status of higher-risk MDS patients at baseline (IWG 2006, IWG 2018)(Cheson et al 2006, Platzbecker 2019). Transfusion independence will be defined as absence of any transfusion during a given period of observation. Furthermore, clarifications about the estimand definition and methods for statistical analyses of PRO data were added. In addition, the need for TLS risk monitoring was further emphasized.

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.

- Glossary of terms: Definition for combination drug was added.
- Protocol Summary: Key Inclusion criteria regarding assessment of eligibility for chemotherapy or stem cell transplantation updated. Key Exclusion criteria amended to exclude patients who received investigational treatment within 5 half-lives of this treatment ; removal of exception of patients with a history of adequately treated malignancy for which no anticancer systemic therapy is ongoing or required during the course of the study. ; and removal of diagnosis of therapy related myeloid neoplasms.
- Section 3 : added statement clarifying that patients receiving treatment in the extension phase are allowed any combination of the treatments.
- Section 4.2 and 4.3.2 : Efficacy and safety data were updated based on new data acquired.
- Section 4.5: Evaluation of risk due to COVID-19 pandemic added.
- Section 4.6 : Rationale for Public Health Emergency mitigations procedures added
- Section 5.1: Inclusion criteria 4 was amended to specify that assessment of eligibility is at time of screening for chemotherapy or stem cell transplantation, and stem cell transplantation was included. Intensive was removed.
- Section 5.2 : Exclusion criteria 5 was amended to exclude patients who received investigational treatment within 5 half-lives of this treatment. Exclusion criteria 14 and 19 amended to exclude patients who received a diagnosis of therapy related myeloid neoplasms or developed therapy related neoplasms.

- Section 6.1.4 : added statement clarifying that patients receiving treatment in the extension phase are allowed any combination of the treatments. Added statement that patients who become eligible for HSCT will be discontinued from MBG453 treatment for clarity in this section.
- Section 6.1.4.1 : Text updated to clarify that continuation of study treatment or components of study treatment beyond progression is not allowed in case of transformation to acute leukemia. Criteria for continuation of study treatment or components of study treatment beyond progression modified. Guidance for assessment of clinical benefit added.
- Section 6.5 : Clarified that the ASCO guidelines include hematologic AEs. Table 6-2: Guidance for non-hematologic, non-immune-related toxicities was amended to clarify that this refers to any non-hematologic, non-immune-related toxicities that are at least possibly attributable to the investigational drug.
- Section 6.5.1 : Added clarification that appendices include additional instructions for the follow-up for toxicities.
- Section 6.7 : Public Health Emergency mitigations procedures added
- Section 7 : Informed Consent will be obtained in case of continuing study treatment or components of the study treatment beyond progression in absence of transformation to acute leukemia. Public Health Emergency mitigations procedures added.
- Section 8 : Public Health Emergency mitigations procedures added.
- Section 8, Table 8-1 : Clarified listing of cytokines are examples. List of cytokines was removed. Clarification added that efficacy bone marrow sample can be an aspirate and/or a biopsy sample. Clarified cycles within the extension phase. Removed requirement of day 30 PKs and IGs within the post-treatment safety FU phase and changed to investigator's discretion.
- Section 8.2 : Clarification added that the last available laboratory results during screening should be used to confirm eligibility. Rationale for collection of subjects' race and ethnicity data added.
- Section 8.3: Transfusion independence and dependence definitions were updated in Table 8-2. In addition, a clarification was added that bone marrow samples, blood smears and pathology reports from the diagnosis should be sent to the central laboratory even if done during regular work-up of the subject before study start.
- Section 8.4 : Public Health Emergency mitigations procedures added.
- Section 8.4.1, Table 8-5: Addition of cytokines types to be analyzed. Collection of Troponin I added as alternative for Troponin T.
- Section 8.4.4: New section added to emphasize monitoring of patients for signs and symptoms of TLS under azacitidine treatment.
- Section 8.5.1 : Public Health Emergency mitigations procedures added.
- [redacted]
- [redacted]
- Section 9.1.1 : Progression of disease (including transformation to acute leukemia) was

added as reason for discontinuation of study treatment, unless criteria to continue study treatment beyond progression as per Section 6.1.5.1 are met. Removed wording for intensive.

- Section 9.1.5 : added statement clarifying that patients receiving treatment in the extension phase are allowed any combination of the treatments. Clarified that patients discontinuing any study treatment other than specified reasons will enter the extension phase. Frequency of survival status calls added.
- Section 10.1.4: Clarification added on process to follow in case of pregnancy.

[redacted]

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

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

Protocol summary:

Title	Single-arm, open label, phase II study of MBG453 (sabatolimab) added to FDA approved Hypomethylating agents of investigator's choice (IV/SC/Oral) for patients with intermediate, high or very high risk myelodysplastic syndrome (MDS) as per IPSS-R criteria (US multi-center) (STIMULUS MDS-US)
Brief title	STIMULUS MDS-US
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Biological
Study type	Interventional
Purpose and rationale	Complete remission with HMAs in patients with intermediate, high, and very high risk MDS is usually infrequent and transient, and prognosis remains poor for these patients. When standard of care based on HMA fails in these patients, treatment options in second line are limited. Main objective of this proposed study is to describe and evaluate safety and efficacy of MBG453 (sabatolimab) 800 mg every 4 weeks on day 8 in combination with FDA approved HMAs of investigator's choice (IV Decitabine or Azacitidine /SC Azacitidine /Oral Decitabine (cedazuridine combination (INQOVI)) (For IV and SC HMAs, sabatolimab (MBG453) can be administered on a day between days 5-8 as per investigator decision)) in a single-arm, non- randomized, open label, phase II multi-center US study.
Primary Objective(s)	To assess the safety profile of MBG453 (sabatolimab) 800 mg (every 4 weeks) given in combination with HMAs (IV/SC/Oral) by 12 months
Secondary Objectives	1. To evaluate complete remission with MBG453 (sabatolimab) in combination with HMAs (IV/SC/Oral) in participants with intermediate, high, or very high risk MDS by 12 months 2. To evaluate PFS rate by 12 months with MBG453 (sabatolimab) combined with HMAs (IV/SC/Oral) in participants with intermediate, high or very high risk MDS 3. To assess Overall Survival rate by 24 months 4. To assess Leukemia-free survival rate by 12 months in each treatment 5. To assess other response rates 6. To assess duration of complete remission 7. To assess time to complete remission 8. To assess the improvement in RBC/platelets transfusion independence
[redacted]	

Study design	This is a single-arm, non- randomized, open label, phase II multi-center study of intravenous MBG453 (sabatolimab) added to FDA approved Hypomethylating agents of investigator's choice (IV/SC/ Oral) in adult participants with intermediate, high or very high risk myelodysplastic syndrome (MDS) as per IPSS-R criteria. There are four separate periods of this study: 1. Screening period (signing of written informed consent through Day 1); 2. Core phase for up to12 months 3. Extension phase for efficacy and/or survival status (up to 12 months after core phase) 4. Post treatment safety follow-up monitoring for adverse events (AEs) for 30 days following the last dose of azacitidine or decitabine or INQOVI (oral decitabine), or 150 days following the last dose of MBG453 (sabatolimab), whichever is later).
Study Population	This target population of this study will be adult patients (≥18 years) to be treated in first-line setting, with intermediate, high or very high risk per IPSS-R prognostic risk categories for myelodysplastic syndrome who do not qualify according the medical judgment for chemotherapy or HSCT. Participants with chronic myelomonocytic leukemia (CMML) are not eligible for this trial. It is anticipated that approximately 39 patients will be enrolled in this study. Patients will be recruited from sites within the United States. Patient population will consist of approximately 39 patients receiving the HMA of choice. No pre-treatment stratification is planned. The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are enrolled in the study.

Inclusion criteria (key)	Written informed consent must be signed by the patient prior to any screening procedures. Patients eligible for this study must meet **all** of the following criteria:
	• Signed informed consent must be obtained prior to participation in the study.
	• Age ≥ 18 years at the date of signing the informed consent form (ICF).
	• Morphologically confirmed diagnosis of a myelodysplastic syndrome (MDS) primary or secondary based on 2016 WHO classification (Arber et al 2016) by investigator assessment with one of the following Prognostic Risk Categories, based on the International Prognostic Scoring System (IPSS-R). Note: MDS diagnosis history will be recorded in the CRF:
	  • Very high (> 6 points)
	  • High (> 4.5 – ≤ 6 points)
	  • Intermediate (> 3 – ≤ 4.5 points)

	• Not suitable at the time of screening for immediate myeloablative/ chemotherapy or hematopoietic stem cell transplantation based on investigator assessment of age, comorbidities, local guidelines, institutional practice (any or all of these). • Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2. • AST and ALT ≤ 3 × upper limit of normal (ULN). • Total bilirubin ≤ 2 × ULN (except in the setting of isolated Gilbert syndrome). • Estimated Glomerular Filtration Rate (eGFR) ≥ 30 mL/min/1.73m2 (estimation based on Modification of Diet in Renal Disease (MDRD) formula, by local laboratory). • Patient is able to communicate with the investigator and has the ability to comply with the requirements of the study procedures.
Exclusion criteria (key)	Patients eligible for this study must not meet **any** of the following criteria: • Prior exposure to TIM-3 directed therapy at any time. Prior therapy with immune checkpoint inhibitors (e.g. anti-CTLA4, anti-PD-1, anti-PD-L1, or anti-PD-L2), cancer vaccines are allowed only if the last dose of the drug was administered more than 4 months prior to enrollment • Previous treatment for intermediate, high or very high risk myelodysplastic syndromes (based on IPSS-R) with chemotherapy or other antineoplastic agents including lenalidomide and hypomethylating agent (HMAs) such as decitabine or azacitidine or INQOVI (oral decitabine) (patients who had up to 1 cycle of HMAs can be included). However, previous treatment with hydroxyurea is permitted. • Diagnosis of acute myeloid leukemia (AML) including acute promyelocytic leukemia and extra-medullary acute myeloid leukemia based on WHO 2016 classification (Arber et al 2016). • Diagnosis of Chronic myelomonocytic leukemia (CMML), or primary or secondary myelofibrosis based on 2016 WHO classification (Arber et al 2016). • History of organ transplant or allogenic hematopoietic stem cell transplant • Participants with prior malignancy, except: a. Participants with history of lower risk MDS treated by supportive care (e.g. growth factors, TGF-beta agents) or untreated are eligible b. Participants with history of lower risk MDS who were treated adequately with lenalidomide and then failed are eligible c. Participants with history of adequately treated malignancy for which no anticancer systemic therapy (namely chemotherapy, radiotherapy or surgery) is ongoing or required during the course of the study. Participants who are receiving adjuvant therapy such as hormone therapy are eligible. • Participants with Myelodysplastic syndrome (MDS) based on 2016 WHO classification (Arber et al 2016) with revised International Prognostic Scoring System (IPSS-R) ≤ 3

Investigational and reference therapy	Primary Product: MBG453 (sabatolimab) Secondary Product: Hypomethylating agents approved in the United States for MDS (IV Decitabine or Azacitidine /SC Azacitidine /Oral Decitabine)
Safety assessments	Incidence and severity of AEs and SAEs, changes in laboratory values and vital signs
Efficacy assessments	1. Complete remission (CR) rate according to International Working Group (IWG) for MDS (2006) * as per investigator assessment by 12 months. 2. PFS rate is defined as time from enrollment to disease progression (including transformation to leukemia per WHO 2016 classification), relapse from CR according to IWG-MDS * or death due to any cause, whichever occurs first, as per investigator assessment ** by 12 months 3. Overall survival rate, time from enrollment to death due to any cause by 24 months. 4. Time from enrollment to ≥ 20% blasts in bone marrow/peripheral blood (per WHO 2016 classification) or death due to any cause 5. Percentage of CR/mCR/PR according to IWG-MDS as per investigator assessment 6. Time from the date of the first documented CR to the date of first documented relapse from CR or death due to any cause, whichever occurs first 7. Time from enrollment to the first documented CR 8. Number and percent of participants who are RBC/platelets transfusion independent after enrollment as per IWG-MDS
Other assessments	1. [redacted] 2. [redacted] 3. A) [redacted] B) [redacted] 4. [redacted] 5. [redacted]
Data analysis	Data from all participating centers will be combined. Data from all centers participating in this study will be aggregated for analyses. Novartis will conduct all analyses and will report data from all centers.

	The study analysis will be by 12 months post last patient first treatment and will be considered the primary analysis, and a CSR will be written. Additional analyses may be performed when all patients complete the extension phase and safety follow up. In this case, a final CSR will be written. All AEs, SAEs and other safety parameters will be summarized. No inferential tests for safety analyses will be performed. All primary, secondary [redacted] will be summarized descriptively. Categorical data will be presented in frequencies and percentages. For continuous data descriptive statistics (mean, standard deviation, median 25th and 75th percentiles, min and max) will be provided. As appropriate, 95% confidence intervals will also be reported. Kaplan Meier's estimates will be reported for the time to event variables. Detail analysis methods will be available in the Statistical Analysis Plan (SAP). Approximately 39 patients will be enrolled for safety and efficacy assessment of this study. Novartis has decided to permanently halt recruitment based on a reevaluation of the development strategy for sabatolimab. Patients who are currently on study treatment or in follow-up may continue per the protocol.
Key words	Phase II, MBG453, TIM-3, decitabine, azacitidine, INQOVI (oral decitabine), myelodysplastic syndrome (MDS).

1 Introduction

1.1 Background

It is estimated that 15,000 to 20,000 new cases of Myelodysplastic Syndromes (MDS) are diagnosed annually in the USA (Klepin 2016). The incidence of MDS is more frequent in male patients and increases with age, with a median age at diagnosis of about 70 years. MDS correspond to a heterogeneous group of hematopoietic diseases that are associated with impaired bone marrow function, ineffective hematopoiesis, elevated bone marrow blasts and persistent peripheral blood cytopenias. Cytogenetics abnormalities are frequently present at time of diagnosis. Patients with MDS have a predisposition to developing acute myeloid leukemia (AML) (Heaney and Golde 1999). Although progression to AML can frequently lead to death in patients with MDS, many deaths are consequences of cytopenias and marrow failure in the absence of leukemic transformation. To account for disease heterogeneity, assess the risk of progression to AML and estimate survival, MDS prognostication systems have been proposed. Prognosis is usually determined using the revised International Prognostic Scoring System (IPSS-R), which considers the percentage of bone marrow blasts, the number of cytopenias, and bone marrow cytogenetics. Patients with untreated MDS are stratified into five IPSS-R prognostic risk categories: very low, low, intermediate, high and very high, with median survival times of 8.8, 5.3, 3.0, 1.6 and 0.8 years, respectively and with 25% AML transformation rate of NR (not reached), 10.8, 3.2, 1.4, 0.73 years respectively (Greenberg et al 2012). In a large database of MDS patients (n = 7,012) distribution of patients across the 5 IPSS-R risk categories were as follows: Very low (19%), low (38%), intermediate (20%), high (13%) and very high (10%) (Greenberg et al 2012). Current treatment guidelines for MDS recommend modification of the disease with hematopoietic stem cell transplantation (HSCT, treatment with a curative intent), hypomethylating agents (HMA: azacitidine or decitabine) or intensive chemotherapy (Fenaux et al 2014). Choice of therapy is mainly driven by the IPSS-R score, the overall general health status and clinical assessment of comorbidities. For patients eligible for intensive therapy, and for whom a donor is available for HSCT or for whom the marrow blast count requires reduction, intensive chemotherapy may be considered (Steensma 2018). HSCT remains the only curative option for MDS patients; however, many MDS patients are not candidate for HSCT (Passweg et al 2011; and see Section 4.3.1). In MDS patients without major co-morbidities who are classified as intermediate, high, very high risk by IPSS-R, and who do not qualify for HSCT or intensive chemotherapy, HMAs remain the first-line reference treatment. HMAs (azacitidine or decitabine) are generally administered for a minimum of 6 cycles (repeat cycle after 4 weeks), and continued for as long as the patient benefits. HMAs (azacitidine or decitabine) have a similar safety profile. In clinical practice, bone marrow suppression is the most common adverse reaction in demethylation therapy, and is also the main reason for the dose-reduction or discontinuations of decitabine or azacitidine. Supportive care, including blood transfusions, is frequently required. HMAs have improved outcomes for patients with intermediate/high risk/very high risk MDS; especially for patients who are not candidates for intensive chemotherapy regiments or HSCT. However, despite these improvements, prognosis for patients treated with HMA remains poor. Complete Remission rate (CR) with azacitidine or decitabine in higher-risk (IPSS; intermediate- & high, IPSS-R; intermediate, high & very high) MDS is rare. CR rate has been shown to be 9% for decitabine and 17 % for azacitidine in pivotal trials (Kantarjian et al 2006, Fenaux et al 2009). Other trials

reported CR rate in MDS patients ranging from 7% to 25% with azacitidine and from 9% to 35% with decitabine. (Saunthararajah 2013).

Zeidan et al reported that azacitidine and decitabine used in monotherapy lead to similar clinical effectiveness and safety profiles retrospective study identified patients diagnosed with MDS between 2004 and 2011 in the US (SEER-Medicare linked database) who received ≥ 10 doses of either HMA for comparing clinical effectiveness in daily practice of azacitidine versus decitabine. Azacitidine was used for treating approximately 80% of the patients (n = 2,025). Survival from HMA initiation was estimated with Kaplan-Meier methods and adjustment was made for relevant covariates. No significant survival difference was found between azacitidine and decitabine in MDS patients, including in MDS patients with excess of blasts. However, it cannot be ruled out treatment outcome of a novel compound given in a combination regimen may vary with nature of the partner drug

Both DEC and AZA require IV infusion for 1 hour or subcutaneous (SC) injections daily for 5-7 days of every 28-day treatment cycle. They both have limited oral bioavailability due to rapid degradation by cytidine deaminase (CDA) in the gut and liver. An orally bioavailable HMA option could reduce clinic visit frequency and reduce infusions/injections related adverse events and burden. ASTX727 is an oral tablet comprised of a fixed-dose combination (FDC) of CDA inhibitor cedazuridine (C) at 100 mg with DEC at 35 mg. In a phase 2 study, INQOVI (oral decitabine) (ASTX727) demonstrated pharmacokinetic (PK) AUC exposure similar to IV-DEC at 20mg/m2 with comparable clinical activity and safety (Garcia-Manero, MDS Int'l symposium, 2019). At ASH 2019 phase 3 study (ASCERTAIN) demonstrated that INQOVI (oral decitabine), the oral FDC of cedazuridine/decitabine (100 mg/35 mg) resulted in an equivalent DEC exposure to IV-DEC at 20 mg/m2 over 5 days. Safety findings are consistent with those anticipated with IV-DEC with no clinically significant GI toxicity. Preliminary clinical activity is also consistent with published data from IV-DEC. INQOVI (oral decitabine) is an oral HMA alternative to IV-DEC (Garcia-Manero et al 2019). The FDA has granted a priority review designation to a new drug application (NDA) for cedazuridine plus decitabine (ASTX727; INQOVI (oral decitabine) for the treatment of adult patients with previously untreated intermediate- and high-risk myelodysplastic syndromes (MDS) or chronic myelomonocytic leukemia (CMML) (accessed at: Astex Pharmaceuticals announces U.S. Food and Drug Administration (FDA). In July 2020, INQOVI has received FDA approval for adult patients with MDS, including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia [CMML]) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups. CC486 (ONUREG) only has data in AML patients and is out of scope for this trial, which is why this molecule was excluded from this study.

Table 1-1 ASTX Oral Decitabine Safety: Most Common All Grades AEs in the First 2 Randomized Cycles (All Causality) – Garcia Manero et al ASH 2019

None of the differences was statistically significant (All P values ≥ 0.10)

GI AEs Grade ≥ 3 incidence <1% for each of ASTX727 and IV decitabine in Cycles 1 or 2

Patients, n (%)	IV Decitabine Cycle 1 or 2 N=132*	ASTX727 Cycle 1 or 2 N=130*
Thrombocytopenia	50 (37.9%)	57 (43.8%)
Neutropenia	42 (31.8%)	46 (35.4%)
Anemia	42 (31.8%)	48 (36.9%)
Fatigue	22 (16.7%)	31 (23.8%)
Constipation	25 (18.9%)	21 (16.2%)
Nausea	21 (15.9%)	23 (17.7%)
Leukopenia	22 (16.7%)	25 (19.2%)
Diarrhea	14 (10.6%)	19 (14.6%)
Febrile neutropenia	10 (7.6%)	18 (13.8%)
Headache	18 (13.6%)	19 (14.6%)

The INQOVI label has updated Adverse Reactions (≥ 10%) in Patients Who Received INQOVI in Pooled Safety Population.

In this trial, participants with higher risk MDS (defined as intermediate risk, high risk & very high risk, will be enrolled. IPSS-R score at baseline is a crucial clinical indicator in the sense it will inform about the treatment outcomes and prognostic of each given Participant. Each level of risk (intermediate/high/very high) is associated with a different survival length and potential of leukemic transformation. From previously reported real world evidence studies, despite the availability of HMA therapies, the risk of death and AML transformation was high. Higher-risk MDS patients had the poorest prognosis, with a median overall survival time less than 1 year from HMA initiation and a median time to AML transformation of less than 2 years from HMA initiation (Stein et al 2019).

Novel targeted therapies and immune checkpoint inhibitors are being clinically studied in MDS. Blocking Programmed cell death protein 1/ligand (PD-1/PD-L1) or Cytotoxic T Lymphocyte Associated Protein 4 (CTLA4) pathways enhances anti-leukemia responses by unleashing Tcells in murine models of AML/MDS. In addition, there is evidence of pharmacodynamic activity and promise for checkpoint inhibition in MDS (Chen et al 2008, Zhang et al 2009, Yang et al 2014, Kong et al 2015, Ørskov et al 2015); however, it will be important to determine the ideal checkpoint inhibitor strategy and to consider combination therapies in order to optimize anti-tumor immunity. A few clinical trials have investigated immune checkpoint inhibitors in MDS and AML patients. An ongoing Phase II study investigates the clinical effects of the checkpoint inhibitors nivolumab (PD1) and ipilimumab (CTLA4) with or without the hypomethylating agent azacitidine in front-line and relapsed MDS patients. Front-line MDS patients were treated with the combination azacitidine+nivolumab or ipilimumab, whereas relapsed MDS patients received single-agent nivolumab or ipilimumab. Twenty patients were treated with azacitidine+nivolumab, 21 with azacitidine+ipilumab, 15 with nivolumab, and 20 with ipilimumab. The observed overall response rate was 75% (15/20), 71% (15/21), 13% (2/15), and 35% (7/20) of patients treated with azacitidine combined with nivolumab,

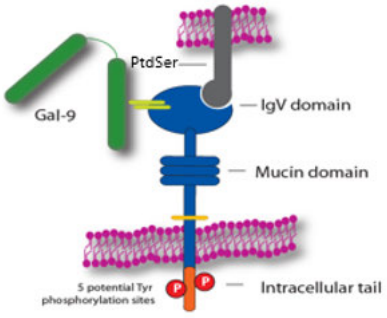
azacitidine combined with ipilimumab, nivolumab, and ipilimumab, respectively; Complete Remission or Complete Remission with residual thrombocytopenia was observed in 10/20 (50%), 8/21 (38%), 0 (0%), and 3 (15%) in patients treated with azacitidine combined with nivolumab, azacitidine combined with ipilimumab, nivolumab, and ipilimumab, respectively.

Main toxicities reported were as follows: skin rash (11%); fatigue (9%); pain (7%); infection (6%); febrile neutropenia (5%); pruritus (6%); diarrhea (5%); constipation, nausea (4% each), alanine aminotransferase (ALT) elevations, anorexia, cough (3% each). This provides preliminary evidence that checkpoint inhibition combined with hypomethylating agents is feasible in front-line MDS and may have clinical activity (Garcia-Manero et al 2018). A Phase Ib/II study involving azacitidine and nivolumab has been conducted in 70 relapsed/refractory AML patients. The overall response rate (ORR) in this study was 33%: 23 clinical responses were reported including 4 complete remission, 11 complete remission with insufficient recovery of counts (CRi), 1 partial remission (PR), and 7 patients with hematologic improvement (HI) maintained > 6 months. The ORR was 58% and 22% in HMA-naive (n = 25) and HMA pretreated (n = 45) patients, respectively. Duration of response among responders was 5.2 months. Three patients in CR/CRi underwent HSCT. Additionally, 6 patients had stable disease lasting for more than 6 months.

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

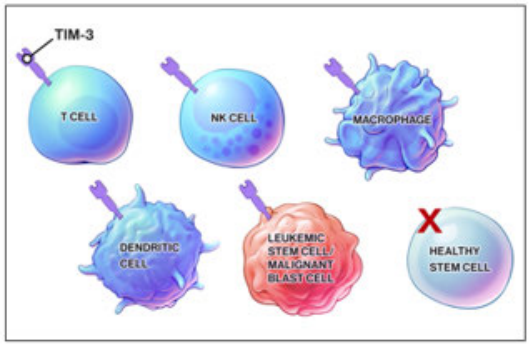
T-cell immunoglobulin and mucin domain-containing 3 (TIM-3) is an inhibitory cell surface receptor with a key role in regulating adaptive and innate immune responses). TIM-3+ hematopoietic stem cells from patients with MDS display aberrant differentiation, increased proliferation and decreased apoptosis (Sakuishi et al 2011). TIM-3 is also preferentially expressed on leukemic stem cells and blasts, and expression of TIM-3 correlates with severity of MDS Therefore the blockade of TIM-3 constitutes a potential target for novel therapies in MDS, and promising preclinical and clinical anti-cancer activity has been reported for TIM-3 blockade (Kikushige et al 2010, Sakuishi et al 2010, Ngiow et al 2011, Sakuishi et al 2011, Jing et al 2015, Asayama et al 2017).

Figure 1-1 TIM-3



TIM-3 is an inhibitory cell surface receptor with a widespread and complex role in immune system regulation, with key roles in: Adaptive immune response (CD4+ and CD8+ effector T cells, regulatory T cells); and Innate immune response (macrophages, DCs, NK cells).

Figure 1-2 TIM-3 Expression



TIM-3 is expressed on the majority of leukemic progenitors in AML (CD34+/CD38- LSCs and CD34+/CD38+ leukemic progenitors), but not on normal HSCs (CD34+/CD38-). TIM-3 expression is seen to correlate with the severity of MDS and progression to AML. TIM-3 activation is involved in LSC self-renewal and activation, as well as immune escape in AML.

MBG453 (sabatolimab) is a high-affinity, humanized anti-TIM-3 IgG4 monoclonal antibody which blocks the binding of TIM-3 to phosphatidylserine (PtdSer) and partially blocks the binding of TIM-3 to Galectin-9.

PK analyses were done in a ph 1-1b/2 study in pts with adv solid tumors (NCT02608268) and a ph 1b study in pts with high/very high risk MDS (HR-MDS) or AML who were ineligible for intensive chemotherapy (NCT03066648). Sabatolimab 400 mg Q2W was predicted to have the highest steady state C_{trough} and TIM-3 occupancy rate when combined with HMA, and 800 mg was predicted to be an equivalent Q4W dosing regimen. No clear relationship was seen between sabatolimab dose or steady state exposure and safety/efficacy at the doses tested. These results support clinical development of the sabatolimab 400 mg Q2W and 800 mg Q4W dosing regimens (Borate et al ASH 2019).

In an early clinical trial, sabatolimab (MBG453) demonstrated a good safety/tolerability profile in pts with advanced solid tumors, also First in human trials have shown that MBG453 can be

safely administered with decitabine in MDS/AML participants suggesting that MBG453 (sabatolimab) may be combined with hypomethylating agents (decitabine or azacitidine) (Borate et al ASH 2019, EHA 2020). Preliminary clinical activity has been observed particularly in high and very high risk MDS participants and an ongoing phase I, II & III studies evaluating MBG453 (sabatolimab) plus decitabine & Azacitidine (IV/SC) in HR-MDS and acute myeloid leukemia (AML).

Therapy-related myelodysplastic syndromes (t-MDS) are defined as MDS occurring as a complication of cytotoxic chemotherapy and/or radiation administered for an antecedent neoplastic or non-neoplastic disorder (Kuendgen et al 2020). Kuendgen et al demonstrated that classification tools established in p-MDS were effective for stratifying subgropus in t-MDS and indicated the high prognostic relevance of cytogenetics in t-MDS.

For further details about sabatolimab (MBG453), refer to the Investigator's Brochure (IB) [MBG453 Investigator's Brochure] & below briefing section.

Ongoing studies with MBG453 (sabatolimab)

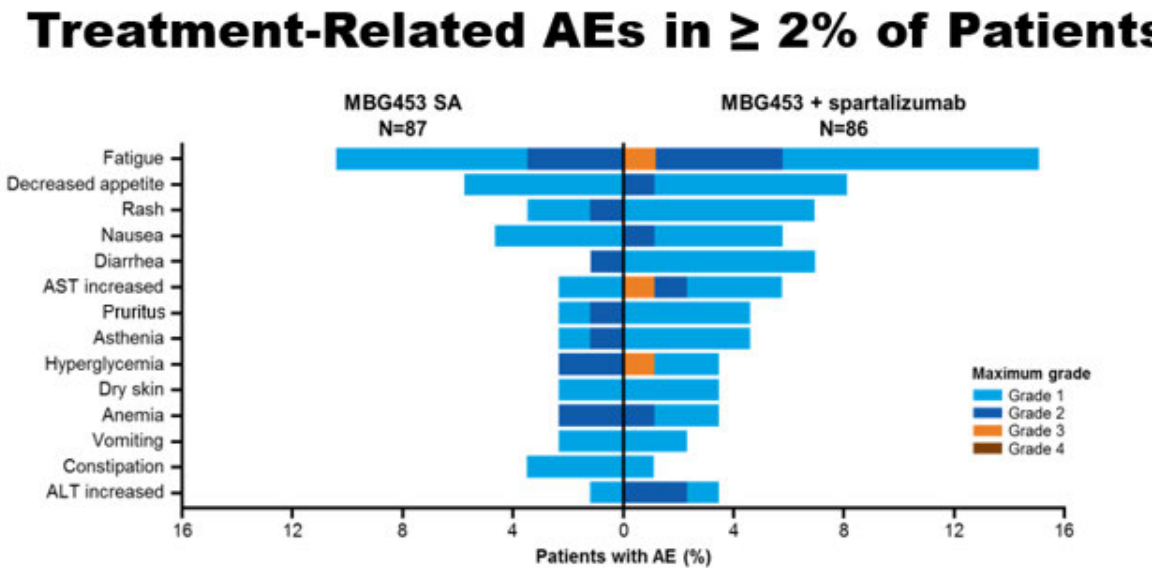
1. There are three Phase I studies involving participants treated with MBG453 (sabatolimab). :
   a. In study [CMBG453X2101 / NCT02608268], 252 participants with solid tumors received MBG453 (sabatolimab) alone or MBG453 (sabatolimab) in combination with PDR001. MBG453 (sabatolimab) single-agent was administered as an IV infusion over 30 minutes at doses ranging from 80 to 1200 mg every 2 weeks (Q2W) or every 4 weeks (Q4W).

Table 1-2 Incidence rates of most frequent AEs with single agent MBG453 (sabatolimab – Solid Tumors

AEs	Single agent of MBG453 (sabatolimab)[2] CMBG453X2101 Solid tumors	
	All-grade AEs	Grade 3/4
Febrile neutropenia	0	0
Thrombocytopenia	2%	0
Neutropenia	1%	0
Nausea	5%	0
Fatigue	9%	0
Anemia	3%	1%

All-AEs suspected, Safety profile (CMBG453X2101) (2019) solid tumor, N=133

Figure 1-3 Treatment-Related AEs in ≥ 2% of Patients



CMBG453X2101. Curigliano G et al. AACR 2019. Oral presentation: CT183

b. In study [CPDR001X2105 / NCT03066648] there were 32 evaluable participants where MBG453 (sabatolimab) was administered as an intravenous (IV) infusion over 30 minutes at doses of 240 mg Q2W, 400 mg Q2W and 800 mg Q4W in combination with decitabine 20mg QD IV for 5 days in participants with AML and high risk MDS.

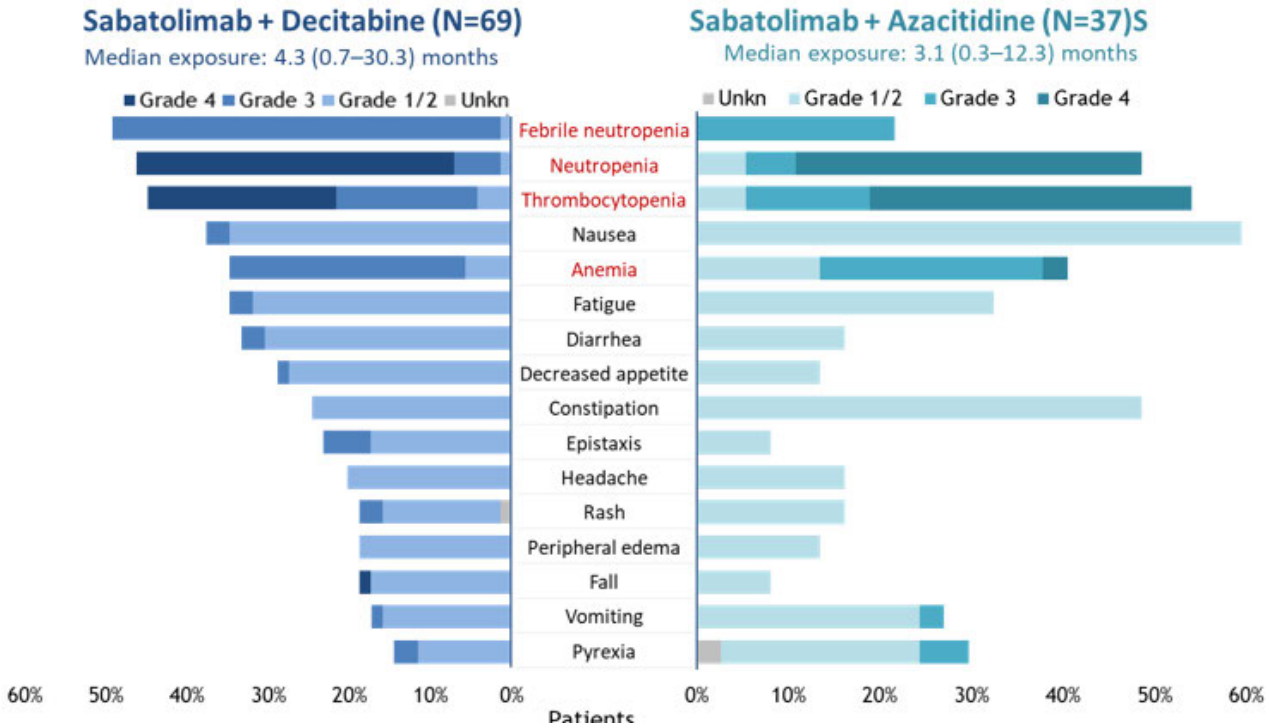
Table 1-3 Incidence rates of most frequent AEs with the Combination MBG453 (sabatolimab) + decitabine)

AEs	PDR001X2105 Combination (MBG453 (sabatolimab)+ decitabine) [1] MDS & AML	
	All-grade AEs	Grade 3/4
Febrile neutropenia	45%	44%
Thrombocytopenia	38%	16%
Neutropenia	35%	17%
Nausea	33%	3%
Fatigue	32%	3%

Anemia	30%	25%

Borate, U et al ASH (2019), PDR001X2105 N=69 including both MDS and AML patients

Figure 1-4 Incidence rates of most frequent AEs with the Combination MBG453 (sabatolimab) + decitabine and MBG453 (sabatolimab) + Azacitidine



Most commonly reported TEAEs were consistent with those for HMA alone; no maximum tolerated dose was reached; no treatment-related deaths occurred ; and treatment discontinuation due to AE occurred in only 4 of 106 patients (2.3%)
Borate, U et al EHA (2020) PDR001X2105 including both MDS and AML patients

Table 1-4 Clinical safety and efficacy in pts with HR-MDS/AML treated with sabatolimab + HMA

	HR-MDS			AML		
Sabatolimab dose	**240 mg Q2W**	**400 mg Q2W**	**800 mg Q4W**	**240 mg Q2W**	**400 mg Q2W**	**800 mg Q4W**
Safety population, n	12	12	15	18	36	23
TEAEs grade ≥3[a] n (%)						
Neutropenia	7 (58.3)	4 (33.3)	7 (46.7)	9 (50.0)	15 (41.7)	10 (43.5)
Thrombocytopenia	9 (75.0)	4 (33.3)	7 (46.7)	4 (22.2)	12 (33.3)	13 (56.5)
Febrile neutropenia	7 (58.3)	3 (25.0)	6 (40.0)	10 (55.6)	11 (30.6)	7 (30.4)
Anemia	5 (41.7)	1 (8.3)	5 (33.3)	3 (16.7)	10 (27.8)	8 (34.8)

Possible treatment-related imAEs grade ≥3[b], n (%)	1 (8.3)	1 (8.3)	0	3 (16.7)	0	1 (4.3)
Efficacy evaluable pts, n	12	12	11	17	24	19
HR-MDS remission rate, n (%)	6 (50.0)	4 (33.3)	6 (54.5)			
CR	2 (16.7)	3 (25.0)	3 (27.3)			
mCR	4 (33.3)	1 (8.3)	3 (27.3)			
PR	0	0	0			
AML remission rate, n (%)				6 (35.3)	9 (37.5)	6 (31.6)
CR				3 (17.7)	4 (16.7)	1 (5.3)
CRi				3 (17.7)	4 (16.7)	3 (15.8)
PR				0	1 (4.2)	2 (10.5)

[a] Most common (≥15% of pts in either the HR-MDS or AML cohort) TEAEs grade ≥3.
[b] A total of 8 such events occurred in 6 pts. Three events (hypothyroidism, infusion-related reaction, and increased ALT) occurred in 1 pt with AML who received sabatolimab 240 mg Q2W. The other 5 events (arthritis, rash, possible HLH, increased ALT, and enterocolitis) each occurred in 1 pt.
CR, complete remission; CRi, CR with incomplete hematologic recovery; imAE, immune-mediated adverse event; mCR, marrow CR; PR, partial remission; TEAE, treatment-emergent adverse event; Q2W, every 2 weeks; Q4W, every 4 weeks.

CMBG453X2101 / NCT02608268 and CPDR001X2105 / NCT03066648 (ASH 2020)

c. As of Oct 2020, in planned study [CMBG453D12101 / NCT04283526] phase Ib for patients with primary myelofibrosis (PMF) or post-polycythemia vera myelofibrosis (PPV-MF) or post-essential thrombocythemia myelofibrosis (PET-MF),the objective of the study is to characterize the safety, tolerability and recommended for each treatment combination (MBG453 + NIS793 ; MBG453 + NIS793 + decitabine ; and MBG453 + NIS793 + spartalizumab).

2. There are two Phase II studies for participants to be treated with MBG453 (sabatolimab) as of Oct 2020 :

a) ongoing CMBG453B12201 (STIMULUS-MDS1 / NCT03946670) Phase II study for intermediate, high and very high risk MDS that included dose of MBG453 (sabatolimab) as 400mg Q2W to be given on day 8 and 22 in addition to HMAs (decitabine 20mg/m2 from D1 to D5 azacitidine 75mg/m2 from D1 to D7 or D1 to D5 + D8 & D9),

b) ongoing CMBG453C12201 (STIMULUS-AML1 / NCT04150029) Phase II study is for AML unfit patients to receive MBG453 (sabatolimab) \ at day 8 in addition to HMAs + venetoclax. In part 1, patients will be enrolled at the starting MBG453 dose level of 400mg Q4W. If deemed safe, additional patients will then be rolled at the second MBG453 dose level of 800mg Q4W. In each cycle, azacitidine will be administered intravenous or subcutaneous at 75 mg/m2 on Days 1 to 5 and Days 8 and 9 (or, at discretion of the investigator on Days 1-7, or Days 1-6 and Day 8 respectively), and venetoclax will be administered orally at 400 mg daily.

3- CMBG453B12301 (STIMULUS-MDS2 / NCT04266301) - A randomized, double-blind, placebo-controlled phase III multi-center study of azacitidine with or without MBG453 (sabatolimab) for the treatment of patients with intermediate, high or very high risk myelodysplastic syndrome (MDS) as per IPSS-R, or Chronic Myelomonocytic Leukemia-2 (CMML-2). To compare OS in participants with intermediate-, high-, or very

high–risk MDS or CMML-2 treated with MBG453 (sabatolimab) 800 mg every 4 week + azacitidine vs. those treated with placebo + azacitidine.

1.2 Purpose

Complete remission with HMAs in patients with intermediate, high, and very high risk MDS is usually infrequent and transient, and prognosis remains poor for these patients. When standard of care based on HMA fails in these patients, treatment options in second line are limited.

Main objective of this proposed study is to describe and evaluate safety and efficacy of MBG453 (sabatolimab) 800 mg every 4 weeks on day 8 in combination with FDA approved HMAs of investigator's choice (IV Decitabine or Azacitidine /SC Azacitidine /Oral Decitabine (cedazuridine combination (INQOVI)) (For IV and SC HMAs, sabatolimab (MBG453) can be administered on a day between days 5-8 as per investigator decision)) in a single-arm, non-randomized, open label, phase II multi-center US study.

2 Objectives and endpoints

Objectives and related endpoints are described in Table 2-1 below.

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective • To assess the safety profile of MBG453 (sabatolimab) 800 mg (every 4 weeks) given in combination with HMAs (IV/SC/Oral) by 12 months	**Endpoint for primary objective** • Incidence and severity of AEs and SAEs, changes in laboratory values and vital signs
Secondary Objectives 1) To evaluate complete remission with MBG453 (sabatolimab) in combination with HMAs (IV/SC/Oral) in participants with intermediate, high, or very high risk MDS by 12 months 2) To evaluate PFS rate by 12 months with MBG453 (sabatolimab) combined with HMAs (IV/SC/Oral) in participants with intermediate, high or very high risk MDS 3) To assess Overall Survival rate by 24 months 4) To assess Leukemia-free survival rate by 12 months 5) To assess other response rates 6) To assess duration of complete remission 7) To assess time to complete remission 8) To assess the improvement in RBC/platelets transfusion independence	**Endpoints for other secondary objectives** 1) Complete remission (CR) rate according to International Working Group (IWG) for MDS (2006) * as per investigator assessment by 12 months. 2) PFS is defined as time from enrollment to disease progression (including transformation to leukemia per WHO 2016 classification), relapse from CR according to IWG-MDS * or death due to any cause, whichever occurs first, as per investigator assessment ** by 12 months post LPFT. 3) Overall survival, time from enrollment to death due to any cause during 12 months post LPFT. 4) Time from enrollment to $\geq$ 20% blasts in bone marrow/peripheral blood (per WHO 2016 classification) or death due to any cause 5) Percentage of CR/mCR/PR according to IWG-MDS as per investigator assessment

Objective(s)	Endpoint(s)
	6) Time from the date of the first documented CR to the date of first documented relapse from CR or death due to any cause, whichever occurs first 7) Time from enrollment to the first documented CR 8) Number and percent of participants who are RBC/platelets transfusion independent after enrollment as per IWG-MDS
[redacted]	

3 Study design

This is a single-arm, non- randomized, open label, phase II multi-center study of intravenous MBG453 (sabatolimab) added to FDA approved Hypomethylating agents of investigator's choice (IV/SC/ Oral) in adult participants with intermediate, high or very high risk myelodysplastic syndrome (MDS) as per IPSS-R criteria.

The primary objective of this study is to assess the safety profile of MBG453 (sabatolimab) 800 mg (every 4 weeks) given in combination with HMAs (IV/SC/Oral) by 12 months.

The following starting doses will be administered: MBG453 (sabatolimab) 800mg every 4 weeks at day 8; and HMAs of investigator choice (INQOVI/oral decitabine: 100mg cedazuridine / 35mg decitabine D1 to D5; IV Decitabine: 20mg/m2 D1 –D5; or Azacitidine IV; or SC: 75 mg/m2 D1 – D7 or D1 to D5 + D8 & D9). (For IV and SC HMAs, sabatolimab (MBG453) can be administered on a day between days 5-8 as per investigator decision)

Study treatment will be administered for 12 months within the core phase of the study (for treatment duration and reasons for discontinuation, please refer to Section 6.1.4 and Section 9.1). After the 12 month core phase, patients may enter the extension phase (based on investigator decision,). For patients that will receive treatment in the extension phase, they are allowed to continue treatment with MBG453 and azacitidine/decitabine/INQOVI (oral decitibine), azacitidine/decitibine/INQOVI (oral decitibine) alone, or MBG453 alone.

In addition, all patients who discontinued any study treatments in the core phase (unless due to progression) may enter the 12 month extension phase. In the extension phase, patients who discontinued any study treatment due to reasons other than progression, death, lost to follow-up, or withdrawal of consent (i.e. transplantation, adverse events, etc.) will have hematology assessments, Patient Reported Outcomes (PRO) and response assessments at defined time points until documented disease progression, death, lost to follow-up, withdrawal of consent, or end of extension phase, whichever comes first (Table 8-1). Patients who progress on study (core phase (first 12 months) or extension phase (additional up to 12 months after the core phase)) will enter the post treatment safety follow up period.

Post treatment follow up is for safety collection and is up to 150 days post core phase or extension phase discontinuation (see Figure 3-1). Survival data will be collected until end of study inclusive of the extension and post treatment follow up duration.

Treatment options and dosing information are provided in Section 6.1. The planned duration of a cycle is 28 days.

Participants who become eligible for hematopoietic stem cell transplant (HSCT) at any time during the course of the study will be discontinued from investigational study treatment (MBG453 (sabatolimab)). [redacted].

All participants must be followed for adverse events (AEs) after the last dose of MBG453 (sabatolimab) as indicated in Section 10.1. All women of child-bearing potential must be followed for pregnancy safety evaluations as per Table 8-1 and after last dose of MBG453 (sabatolimab) as indicated in Section 10.1.4.

At the end of the study, every effort will be made, in alignment with local regulations, to continue provision of MBG453 (sabatolimab) outside this study through an alternative setting to participants who are receiving treatment with MBG453 (sabatolimab) and in the opinion of the investigator are still deriving clinical benefit. Options for continued treatment with MBG453 (sabatolimab) may include access to commercially available drug, or managed access program, or a roll-over study.

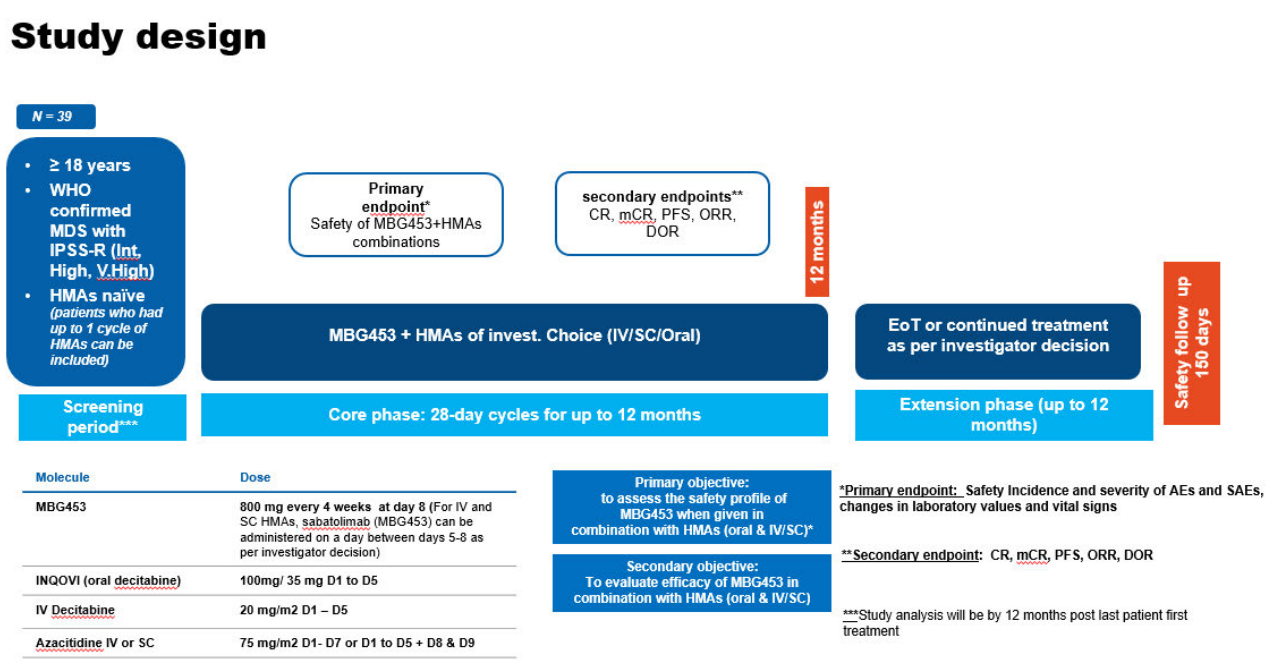
[redacted]

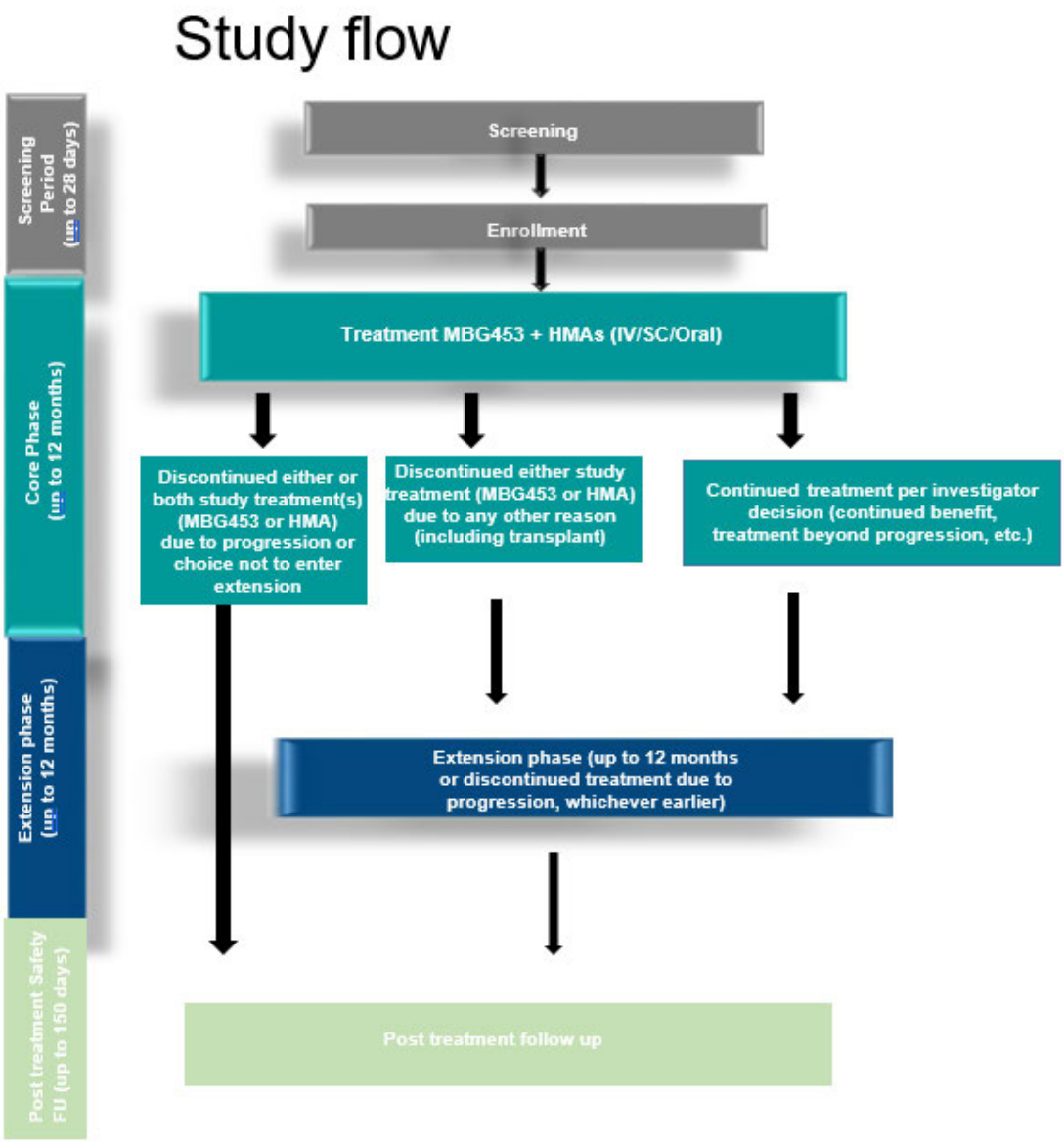
There are four separate periods of this study:

1. Screening period (signing of written informed consent through Day of enrollment);
2. Core phase for up to12 months
3. Extension phase for efficacy and/or survival status (up to 12 months after core phase)
4. post treatment safety follow-up monitoring for adverse events (AEs) for 30 days following the last dose of azacitidine or decitabine or INQOVI (oral decitabine), or 150 days following the last dose of MBG453 (sabatolimab), whichever is later.

Approximately 39 patients who are evaluable for primary endpoints will be assessed.

Figure 3-1 Study design





3.1 Definition of end of study

The end of the study (Last Patient Last Visit) is defined as once all patients discontinued study treatment and were transitioned to treatment outside the study and have completed the study which is targeted at the latest 29 months after the last patient was enrolled. The Last Patient Last Visit will include all the required safety follow-up visits.

4 Rationale

4.1 Rationale for study design

The justification for a single arm, non-randomized phase II trial is to determine the safety of adding MBG453 (sabatolimab) every 4 weeks at day 8 to oral HMAs & at day 8 for IV and SC HMAs (For IV and SC HMAs, sabatolimab (MBG453) can be administered on a day between days 5-8 as per investigator decision) to on the primary safety & secondary efficacy endpoints

This prospective, non- randomized, study design of MBG453 (sabatolimab) combined with oral HMA (decitabine) complements other randomized placebo controlled MBG453 (sabatolimab) + IV/ SC HMAs development studies.

In this trial, participants with higher risk MDS (defined as very high risk, high risk, intermediate risk) will be enrolled. The choice of HMA (IV/SC/Oral) is left to the investigator's discretion in order to reflect the local approval and the local clinical practice. IPSS-R score at baseline is a crucial clinical indicator in the sense it will inform about the treatment outcomes and prognostic of each given Participant. Each level of risk (intermediate/high/very high) is associated with a different survival length and potential of leukemic transformation (see Section 1.1). Azacitidine and decitabine used in monotherapy lead to similar clinical effectiveness and safety profiles (see Section 1.1). However, it cannot be ruled out treatment outcome of a novel compound given in a combination regimen may vary with nature of the partner drug.

The primary goal for treatment of higher-risk MDS patients (pts) is to improve overall survival (OS) and delay acute myeloid leukemia (AML) evolution. The IWG 2006 response criteria are used in clinical trials and in clinical practice for assessing efficacy of MDS therapies. These criteria were originally proposed by an international group of experts based on available data and consensus. In an ad hoc landmark analysis of the AZA-001 study using the 2006 IWG criteria, patients who achieved hematological improvement (HI), complete response (CR), marrow CR (mCR), or partial response (PR) demonstrated improved OS.

Treatment response by IWG 2006 criteria and correlation with clinical outcomes has been evaluated in studies (Blood 2015, Leukemia Research 2016). In a study conducted with data from the MDS Clinical Research Consortium, HR-MDS patients treated with HMA who achieved CR had a longer median OS, as compared to patients who achieved PR, SD or HI (Leukemia Research 2016).

Due to its correlation with overall survival, the emerging goal for HR-MDS is to achieve complete remission (the bone marrow and blood cell counts return to normal). Only 40% to 50% of patients typically will respond to HMAs, with a median duration of response < 1.5 years and eventually all patients will lose initial response. Outcome after HMA treatment failure is poor and represents an unmet need. Complete remission (CR) have shown to be associated with prolonged overall survival in MDS patients (Komrokji 2015).

In Komrokji 2015 study AZA001, for patients who were treated with HMA as first line therapy, the best response rates by IWG 2006 criteria were CR in 15%.

In Garcia-Manero ASH 2019, CR rate for HR MDS/CMML study the oral decitabine data shows CR as 12%.

4.2 Rationale for dose/regimen and duration of treatment

The proposed MBG453 (sabatolimab) dose in the study is 800 mg Q4W based on data accumulated from two phase I studies: [CMBG453X2101] and [CPDR001X2105]. [CMBG453X2101] in solid tumor patients has a wide MBG453 (sabatolimab) dose range (single agent MBG453 (sabatolimab) from 80 to 1200 mg every 2 weeks (Q2W) or every 4 weeks (Q4W), with a lower 20 mg Q2W MBG453 (sabatolimab) dose additionally tested in combination with PDR001. Because of the data obtained in [CMBG453X2101], study [CPDR001X2105] started evaluating MBG453 (sabatolimab) at 240 mg Q2W and additionally tested 400 mg Q2W and 800 mg Q4W in combination with decitabine.

Clinical Pharmacology: The pharmacokinetics (PK) of MBG453 (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 MBG453 (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. The 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 and 800 mg Q4W in combination with hypomethylating agents, with CR or marrow CR in higher risk MDS participants and CR or CRi in newly diagnosed AML participants. Among responding higher-risk MDS participants, there were durable responses as long as 30 months (see section 4.3.2. No dose-response relationship was observed. In a preliminary exposure-response analysis, there was also no clear relationship between exposure and response, using steady state exposure metrics of AUCtau or Ctrough and efficacy metrics of clinical benefit (CR/mCR/CRi) or percent blast cell reduction.

Clinical Safety: In study [CMBG453X2101], as of 25-Jul-2019, a total of 133 participants with solid tumors have been treated with MBG453 (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 (4.5% 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 MBG453 (sabatolimab) as a single agent (n=26) or in combination with decitabine (n=81) or azacitidine (n=16). In the 26 participants treated with MBG453 (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 MBG453 (sabatolimab) in combination with decitabine, the most frequent adverse events (all grades, >10%) attributed to study treatment have included thrombocytopenia, anemia,

neutropenia, nausea, and fatigue. One participant experienced a DLT during the first 2 cycles, which consisted of hepatitis manifesting as Grade 3 ALT increase. One participant discontinued study treatment due to a treatment-related AE of possible hemophagocytic lymphohistiocytosis. In the 16 participants treated with MBG453 (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, 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 potentially immune related adverse events, providing additional support for 800 mg Q4W regimen which has the highest Cmax among the doses tested. Please refer to the [MBG453 (sabatolimab) Investigator's Brochure] for additional information of AEs reported in participants with solid tumors or with hematologic malignancies treated with MBG453 (sabatolimab) as a single agent or in combination with other drugs.

As per the latest data analysis (cut-off: 10-Apr-2020) of HR-MDS and AML patients treated with MBG453 + HMA combination; including 69 patients treated with MBG453+decitabine and 37 patients treated with MBG453+azacitidine combination from study [CPDR001X2105], MBG453 + HMA combination was safe and well tolerated. No Maximum Tolerated Dose (MTD) was reached and no new significant safety issues were observed. Most commonly reported treatment emergent adverse events were consistent with those for HMA alone. The majority (92%) of possible immune mediated adverse events (imAEs) related to study treatment were grade 1/2. No treatment related deaths were reported.

Predicted target engagement: A population pharmacokinetic model of MBG453 (sabatolimab) concentration was fit to all participants from both studies to the predicted TIM-3 occupancy in the bone marrow by making assumptions about MBG453 (sabatolimab) biodistribution to the bone marrow and binding to TIM-3. Using trial simulation, this model predicted that the 800 mg Q4W dose would give at least 95% receptor occupancy in at least 95% of participants at steady state Ctrough. This high degree of target engagement is also supported by a plateau in the accumulated soluble TIM-3 that is observed at doses of 240 mg Q2W and above, and at 800 mg Q4W and above.

In summary, given the excellent safety and tolerability seen across all doses and schedules in [CMBG453X2101] and [CPDR001X2105], the activity seen at all 3 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 a clear dose-response or exposure-response relationship for MBG453 (sabatolimab), 800 mg Q4W was selected as the dose regimen for this study.

4.3 Rationale for choice of the combination drugs

4.3.1 Rationale for HMA (IV/SC azacitidine or IV/oral decitabine)

In MDS patients, HSCT is the only curative option. However, only a minority of MDS patients are candidates for HSCT and the intensive chemotherapy, which may be used prior to transplant (Steensma 2018, Platzbecker 2019).

Treatment strategies are generally non-intensive and risk-adapted (by IPSS-R), ranging from watchful surveillance, iron chelation and growth factors to lenalidomide and HMA.

Higher risk MDS patients who are non-transplant candidates are commonly treated with HMA therapy. HMAs (azacitidine and decitabine) represent the only approved therapeutic agents and constitute the current standard or care. Patients continue treatment if tolerated as long as they benefit. The main treatment goal is to delay or avoid disease progression and transformation to acute leukemia.

Both drugs (decitabine and azacitidine) are approved in the USA, whereas only azacitidine is approved for treating higher risk MDS in Europe. The pivotal Phase III trial of azacitidine (Fenaux et al 2009) reported a statistically significant survival benefit (median overall survival 24.5 months versus 15.0 months) of azacitidine compared to conventional care including intensive chemotherapy. Decitabine approval in the US is mainly based on the findings from a Phase III clinical trial which demonstrated decitabine-treated participants achieved a significantly higher overall response rate (17%), including 9% complete remissions, compared with supportive care (0%) ($p < 0.001$). An additional 12 participants who were treated with decitabine (13%) achieved hematologic improvement. Responses were relatively durable (median, 10.3 mos.) and were associated with transfusion independence (Kantarjian et al 2006). Azacitidine and decitabine have not been compared in clinical trials. However, a large retrospective study identified patients diagnosed with MDS between 2004 and 2011 in the US (SEER-Medicare linked database) who received $\geq$ 10 doses of either HMA for comparing clinical effectiveness in daily practice of azacitidine versus decitabine. Azacitidine was used for treating approximately 80% of the patients (n = 2,025). Survival from HMA initiation was estimated with Kaplan-Meier methods and adjustment was made for relevant covariates. No significant survival difference was found between azacitidine and decitabine in MDS patients, including in MDS patients with excess of blasts (Zeidan et al 2016).

Safety profiles of decitabine and azacitidine are similar. Azacitidine and decitabine are generally well tolerated and both have a manageable toxicity profile (Derissen et al 2013). The most common toxicity is myelosuppression, primarily neutropenia and thrombocytopenia. Adverse events related to myelosuppression typically occur in the third week of the treatment cycle and participants commonly achieve hematologic recovery prior to the next treatment cycle. Otherwise, a delay in starting the next cycle or a dose reduction may be necessary. During the clinical trials, hematologic adverse events were most frequently observed during the first two treatment cycles and nadir values for hematological parameters improved during subsequent cycles. The most common non-hematological adverse events corresponded to gastrointestinal toxicities (nausea, vomiting, diarrhea, and constipation) which generally occurred in the first week of the treatment cycle. These events were generally mild and transient. They could be managed with concomitant medications, including antiemetics and antidiarrheal.

Azacitidine and decitabine regimens used in this trial are the most studied regimens and recommended by international treatment guidelines.

In a phase 2 study, INQOVI (oral decitabine) (ASTX727) demonstrated pharmacokinetic (PK) AUC exposure similar to IV-DEC at 20mg/m2 with comparable clinical activity and safety (Garcia-Manero, MDS Int'l symposium, 2019). At ASH 2019 phase 3 study (ASCERTAIN) demonstrated that INQOVI (oral decitabine), the oral FDC of cedazuridine/decitabine (100 mg/35 mg) resulted in an equivalent DEC exposure to IV-DEC at 20 mg/m2 over 5 days. Safety findings are consistent with those anticipated with IV-DEC with no clinically significant GI toxicity. Preliminary clinical activity is also consistent with published data from IV-DEC. INQOVI (oral decitabine)is an oral HMA alternative to IV-DEC (Garcia-Manero et al 2019). The FDA has granted a priority review designation to a new drug application (NDA) for cedazuridine plus decitabine (ASTX727; INQOVI) for the treatment of adult patients with previously untreated intermediate- and high-risk myelodysplastic syndromes (MDS) or chronic myelomonocytic leukemia (CMML).(accessed at: Astex Pharmaceuticals announces U.S. Food and Drug Administration (FDA); According to research presented as a late-breaking abstract at the 2019 ASH Annual Meeting, treatment with CC-486, an oral formulation of the hypomethylating agent azacitidine, improved overall survival (OS) and relapse-free survival (RFS) when used as maintenance therapy in patients with acute myeloid leukemia (AML) who were in remission after induction chemotherapy.

These efficacy results suggest that CC-486 could represent a new standard in this setting (post remission AML maintenance); however considering difference in pharmacokinetics between CC-486 & IV Azacitidine in addition to no current studies in Higher risk MDS – there are no plans for HR-MDS label inclusion for this molecule. (Garcia- Manero et al 2008, Cogle et al 2015).

Table 4-1 ASTX Oral Decitabine Safety: Most Common All Grades AEs in the First 2 Randomized Cycles (All Causality) – Garcia Manero et al ASH 2019

None of the differences was statistically significant (All P values ≥ 0.10)

GI AEs Grade ≥ 3 incidence <1% for each of ASTX727 and IV decitabine in Cycles 1 or 2

Patients, n (%)	IV Decitabine Cycle 1 or 2 N=132*	ASTX727 Cycle 1 or 2 N=130*
Thrombocytopenia	50 (37.9%)	57 (43.8%)
Neutropenia	42 (31.8%)	46 (35.4%)
Anemia	42 (31.8%)	48 (36.9%)
Fatigue	22 (16.7%)	31 (23.8%)
Constipation	25 (18.9%)	21 (16.2%)
Nausea	21 (15.9%)	23 (17.7%)
Leukopenia	22 (16.7%)	25 (19.2%)
Diarrhea	14 (10.6%)	19 (14.6%)
Febrile neutropenia	10 (7.6%)	18 (13.8%)
Headache	18 (13.6%)	19 (14.6%)

In July 2020, INQOVI has received FDA approval for adult patients with MDS, including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia [CMML]) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups. Oral decitabine is also included within the NCCN guidelines.

4.3.2 Rationale for MBG453 (sabatolimab)

The large family of costimulatory molecules plays a crucial role in regulation of the immune response. These molecules modulate the immune system by phosphorylation cascades. Some of the coinhibitory members of this family, such as PD-1 and CTLA-4, already constitute clinical targets in oncology and, since 2011, have opened a new area of antitumor immunotherapy. Checkpoint inhibitors (such as nivolumab, ipilimumab, pembrolizumab) have been approved by health authorities (FDA and EMA in particular) for numerous cancer indications including hematologic malignancies, and they are used in daily clinical practice. A great deal of clinical trials are ongoing to assess these antibodies in new potential indications. Many novel antibodies targeting inhibitory receptors (such as e.g. TIM-3, VISTA, Lag-3) or activating costimulatory molecules (such as OX40, GITR) are also being investigated in clinical trials enrolling participants with solid tumors or hematological malignancies.

Abnormal upregulation of PD-L1, PD-L2, PD-1, and CTLA4 in CD34+ cells in MDS participants compared to healthy controls has been reported (Yang et al 2014), and their expression is further upregulated following epigenetic therapy with HMAs. Overexpression of these checkpoint receptors on T cells and ligands on AML/MDS blasts interferes with effective T- cell antitumor response and is associated with leukemic progression in preclinical models. Novel monoclonal antibodies targeting CTLA-4 (e.g. ipilimumab) or PD-1/PD-L1 (e.g. nivolumab, pembrolizumab, and atezolizumab) can reverse immune suppression and enables lymphocyte-mediated toxicity against blasts. Results of ongoing early clinical trials evaluating these agents in monotherapy or in combination with the hypomethylating agents in relapsed AML and frontline post-hypomethylating MDS are showing promising clinical activity and acceptable safety profile in participants treated with these agents alone or in combination to HMA (see Section 1.1).

Similarly to PD1 and CTLA4, MDS patients overexpress the immune checkpoint receptor, TIM-3, which inhibits immune recognition by cytotoxic T cells (Kikushige et al 2010). TIM-3 expression levels on MDS blasts increases as MDS progresses to the advanced stage. It has been observed that the proliferation of TIM-3 + MDS blasts is inhibited by the blockade of TIM-3 using an anti-TIM-3 antibody (Asayama et al 2017). Hence, TIM-3 constitutes a relevant target for novel therapies in development in MDS and AML. MBG453 (sabatolimab) is a high-affinity, ligand-blocking, humanized anti-TIM-3 IgG4 antibody (stabilized hinge, S228P) which blocks the binding of TIM-3 to phosphatidylserine (PtdSer). Clinical trials of MBG453 (sabatolimab) are ongoing in solid tumors and hematological malignancies.

Safety data indicate that the compound was well tolerated overall in 291 participants with solid tumors or hematological malignancies exposed to MBG453 (sabatolimab). Two trials are ongoing as of Oct 2020: one Phase I/II open label, multicenter study of the safety and efficacy of MBG453 (sabatolimab) as single agent and in combination with PDR001 in adult participants

with advanced malignancies [CMBG453X2101] and a Phase Ib multi-arm, open label study of PDR001 and/or MBG453 (sabatolimab) in combination with decitabine in participants with AML or high risk MDS [CPDR001X2105].

In particular, the compound was well tolerated as a single agent or when it is administered intravenously in combination with decitabine to MDS/AML participants. Please refer to Section 1.1 and the [MBG453 (sabatolimab) Investigator's Brochure] for more details.

Preliminary efficacy data reported in study [PDR001X2105] with higher risk MDS participants are showing high response rates. At the time of the latest analysis (cut-off: 10-Apr-2020), in the MBG453 + decitabine arm, 11 of 18 (61.1%) evaluable high risk and very high risk MDS patients have achieved a response (6 complete remissions [33.3%], 3 marrow complete remissions [16.7%], 2 stable diseases with hematologic improvement [11.1%]). Median of exposure in this arm is approximately 8 months. Durability of response and clinical benefit is being observed with the longest responding higher-risk MDS subjects continuing on study for more than 30 months. In the MBG453 + azacitidine arm, 11 of 19 (57.9%) evaluable higher-risk MDS patients have achieved a response (2 complete remissions [10.5%], 7 marrow complete remissions [36.8%], 2 stable diseases with hematologic improvement [10.5%]). Of note, data from this arm is less mature with duration of follow-up of approximately 3 monthsRationale for combining MBG453 (sabatolimab) with HMA (IV/ SC azacitidine and IV/ oral decitabine)

Despite the fact that single-agent HMAs are available for the treatment of patients with higher risk MDS, alternative treatment strategies are urgently needed; because achieving complete remission with HMA alone in this difficult to treat population is a rare event and the duration of the clinical benefit is commonly transient. Furthermore, attempts to use HMA single-agent to increase the HSCT rate or as alternative treatment of cytarabine in higher risk MDS patients have been disappointing. In addition, many higher risk MDS patients eventually progress on HMAs and ultimately progress to AML.

Combining HMAs with novel agents may improve their clinical efficacy and overcome resistance. The fact that immune checkpoint inhibitors have been able to generate deep and durable response in various cancers including hematologic malignancies together with emerging preclinical and clinical data (see Section 15) strongly supports the evaluation of the novel anti-TIM-3 antibody MBG453 (sabatolimab) combined with HMAs in MDS.

Preclinical data suggest HMA enhances checkpoint expression and that a synergistic response may be produced by using a checkpoint inhibitor and a hypomethylating agent concomitantly. HMAs induce increased expression of other checkpoints in MDS patients, i.e. PD-1, PD-L1, PD-L2 and CTLA4, which may justify the use of check-point inhibitors in combination with HMAs (Yang et al 2014, Ørskov et al 2015). Another interesting biological finding is that demethylation of the TIM-3 promoter has been shown to be critical for the stable expression of TIM-3 on T cells, indicating that modulation of the expression of TIM-3 by hypomethylating agents (azacitidine or decitabine) could have important immunomodulatory implications (Chou et al 2016). Furthermore, decitabine has been shown to increase the activity of Natural Killer (NK) cells, which may play a role in anti-tumor immunity (Sohlberg et al 2015).

Emerging clinical data from the ongoing Phase I study [CPDR001X2105] enrolling high risk MDS Participants indicate that MBG453 (sabatolimab) plus decitabine combination is feasible,

well tolerated and produces clinical responses (see Section 4.3.2). Please refer to Section 4.2 and to the [MBG453 (sabatolimab) Investigator's Brochure] for more details.

Azacitidine and decitabine exhibit a similar safety profile and share a similar mechanism of action. As a result, the combination of MBG453 (sabatolimab) with azacitidine is likely to be feasible and as tolerated as the combination MBG453 (sabatolimab) with decitabine. Immunomodulators, such as MBG453 (sabatolimab), may regulate CYP enzymes and may cause Drug-Drug Interaction (DDI) with small molecule drugs because of the potential to alter CYP mediated metabolism. However, cytochrome P450 mediated degradation is minor for HMA and therefore DDI between MBG453 (sabatolimab) and HMA is not expected. When MBG453 (sabatolimab) was administered in combination with decitabine in the CPDR001X2105 study, MBG453 (sabatolimab) PK were similar to that observed in the CMBG453 X2101 study, while decitabine PK was similar to the label reported value.

In CPDR001X2105 study, a signal of a relevant clinical activity is being reported with high response rate, durable response and absence of disease progression in all high risk MDS and newly diagnosed AML participants who were treated (see above).

Serious suspected cases of pneumonitis (1 case from CPDR001X2105 in a ND-AML patient and 2 blinded cases from CMBG453B12101 in HR-MDS patients) have been reported in combination with hypomethylating agents. Additionally, one serious potential pneumonitis case was reported from CHDM201H12101C study in an AML patient treated with MBG453 in combination with another investigational agent (HDM201, p53/MDM2 inhibitor).

This US multi-center study will generate complementary data for the ongoing sabatolimab + IV/SC HMA trials. In addition it will evaluate these combination in secondary MDS as it is currently excluded.

Both DEC and AZA require IV infusion for 1 hour or subcutaneous (SC) injections daily for 5-7 days of every 28-day treatment cycle. They both have limited oral bioavailability due to rapid degradation by cytidine deaminase (CDA) in the gut and liver. An orally bioavailable HMA option could reduce clinic visit frequency and reduce infusions/injections related adverse events and burden. INQOVI (oral decitabine) is an oral tablet comprised of a fixed-dose combination (FDC) of CDA inhibitor cedazuridine (C) at 100 mg with DEC at 35 mg.

None of the Novartis registration trials allow for the use of oral decitabine since it was just recently approved. Study rationale is to generate data for MBG452 and recently FDA approved and NCCN included INQOVI (oral decitabine).

[redacted]

4.4 Purpose and timing of interim analyses

As appropriate, interim analyses may be performed for publication or any regulatory purpose.

The study primary analysis will be by 12 months post last patient first treatment and a CSR will be written. Additional Final Analysies may be performed when all patients complete the extension phase and safety follow up. In this case, the final CSR will be written.

4.5 Risks and benefits

The potential benefit of MBG453 (sabatolimab) combined with HMA in MDS is suggested by early efficacy results from the study [PDR001X2105], which showed achievement of durable complete remission or bone marrow CR in high risk MDS participants receiving MBG453 (sabatolimab) in combination with decitabine (Section 4.3.2). The proportion of higher-risk MDS patients achieving CR/mCR and durable CR/mCR under treatment with MBG453 (sabatolimab) combined with decitabine appears to be larger as compared to historic and published data on similar MDS patients treated with decitabine or azacitidine alone.

The risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring. The MBG453 (sabatolimab) dose established in other studies will be used in combination with HMA, dose modifications must be applied per protocol based on clinical or laboratory findings, and a close safety monitoring will be performed during the study.

Occurrence of an immune-related event is an anticipated risk in participants treated with checkpoint inhibitors, such as MBG453 (sabatolimab). In the case of an immune-related event,

there are dose modification and management guidelines, including for follow-up of toxicities, proposed by the protocol in relation to recent American Society of Clinical Oncology (ASCO) practices guidelines about management of immune-related adverse events in patients treated with checkpoint inhibitors (Brahmer et al 2018; see Section 6.5). Additionally, general guideline for non-hematologic non-immune-related toxicities that are clinically significant per investigator judgement and that are possibly attributable to the investigational drug is also provided (see Table 6-3).

The feasibility of starting a new clinical trial during a pandemic situation was assessed. The MBG453 (sabatolimab) benefit / risk ratio remains unchanged in light of the COVID-19 pandemic. If a patient becomes infected with the virus, we recommend the patient recover before restarting the study drug.

Based on single agent data, there are no expected significant overlapping toxicities between INQOVI (oral decitabine) and MBG453 (sabatolimab) combination. Based on currently available data from phase I, there are no known significant overlapping toxicities between IV decitabine or IV/SC azacitidine and MBG453 (sabatolimab). However, there may be unforeseen risks from combining decitabine or INQOVI (oral decitabine) or azacitidine with MBG453 (sabatolimab), which could be serious. In particular, since one focus of this study is to combine immunomodulatory agents in order to increase the anti- tumor immune response, there is the potential for increased toxicity secondary to increase in cytokine release syndrome due to activation of T cells and macrophages, and there may also be changes in immune function that could lead to increased autoimmunity or risk of infection or risk of immune-related adverse events. All participants enrolled will be monitored closely for these potential toxicities.

Women of child-bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and 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.

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

Approved HMAs labels are available at FDA website and MBG453 (sabatolimab) Investigator Brochure will be provided to sites as updates occur.

4.6 Rationale for Public Health Emergency mitigations procedures

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Study Population

This target population of this study will be adult patients (≥18 years) to be treated in first-line setting, with intermediate, high or very high risk per IPSS-R prognostic risk categories for myelodysplastic syndrome who do not qualify according the medical judgment for chemotherapy or HSCT. Participants with chronic myelomonocytic leukemia (CMML) are not eligible for this trial.

It is anticipated that approximately 39 patients will be enrolled in this study. Patients will be recruited from sites within the United States.

Patient population will consist of approximately 39 patients receiving the HMA of choice that is approved for frontline higher risk MDS. No pre-treatment stratification is planned. Post study sub-group exploratory analysis will be evaluated. The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are enrolled in the study.

5.1 Inclusion criteria

Written informed consent must be signed by the patient prior to any screening procedures. Patients eligible for this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study.
2. Age ≥ 18 years at the date of signing the informed consent form (ICF).
3. Morphologically confirmed diagnosis of a myelodysplastic syndrome (MDS) primary or secondary based on 2016 WHO classification (Arber et al 2016) by investigator assessment with one of the following Prognostic Risk Categories, based on the International Prognostic Scoring System (IPSS-R). Note: MDS diagnosis history will be recorded in the CRF:
   - Very high (> 6 points)
   - High (> 4.5 – ≤ 6 points)
   - Intermediate (> 3 – ≤ 4.5 points)
4. Not suitable at time of screening for immediate myeloablative/ chemotherapy or hematopoetic stem-cell transplantation based on investigator assessment of age, comorbidities, local guidelines, institutional practice (any or all of these).
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2.
6. AST and ALT ≤ 3 × upper limit of normal (ULN).
7. Total bilirubin ≤ 2 × ULN (except in the setting of isolated Gilbert syndrome).
8. Estimated Glomerular Filtration Rate (eGFR) ≥ 30 mL/min/1.73m2 (estimation based on Modification of Diet in Renal Disease (MDRD) formula, by local laboratory).
9. Patient is able to communicate with the investigator and has the ability to comply with the requirements of the study procedures.

5.2 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Prior exposure to TIM-3 directed therapy at any time. Prior therapy with immune checkpoint inhibitors (e.g. anti-CTLA4, anti-PD-1, anti-PD-L1, or anti-PD-L2), cancer vaccines are allowed only if the last dose of the drug was administered more than 4 months prior to enrollment.
2. Previous treatment for intermediate, high or very high risk myelodysplastic syndromes (based on IPSS-R) with chemotherapy or other antineoplastic agents including lenalidomide and hypomethylating agent (HMAs) such as decitabine or INQOVI (oral decitabine) or azacitidine (patients who had up to 1 cycle of HMAs can be included). However, previous treatment with hydroxyurea is permitted.
3. History of severe hypersensitivity reactions to any ingredient of study drug(s) (azacitidine, decitabine, INQOVI (oral decitabine) or MBG453 (sabatolimab)) or monoclonal antibodies (mAbs) and/or their excipients.
4. Current use or use within 14 days prior to enrollment of systemic, steroid therapy (>10 mg/day prednisone or equivalent) or any immunosuppressive therapy. Topical, inhaled, nasal, ophthalmic steroids are allowed. Replacement therapy, steroids given in the context of a transfusion are allowed and not considered a form of systemic treatment.
5. Investigational treatment for MDS received within 4 weeks or 5 half-lives of this investigational treatment, whatever is longer prior to enrollment. In case of a checkpoint inhibitor: 4 months minimum prior to enrollment interval is necessary to allow enrollment.
6. Active autoimmune disease requiring systemic therapy (e.g. corticosteroids).
7. Live vaccine administered within 30 days prior to enrollment. (refer to Exclusion criteria 1 regarding cancer vaccines)
8. Treatment with drugs that are metabolized by cytidine deaminase within 7 days prior to starting the study treatment.
9. Diagnosis of acute myeloid leukemia (AML) including acute promyelocytic leukemia and extra-medullary acute myeloid leukemia based on WHO 2016 classification (Arber et al 2016).
10. Diagnosis of Chronic myelomonocytic leukemia (CMML), or primary or secondary myelofibrosis based on 2016 WHO classification (Arber et al 2016).
11. History of organ transplant or allogenic hematopoietic stem cell transplant
12. Any concurrent severe and/or uncontrolled medical condition. Participants with active infection requiring parenteral antibacterial, antiviral or antifungal therapy which are controlled by treatment are eligible.
13. Cardiac or cardiac repolarization abnormality, including but not limited to any of the following,:
    a. History of myocardial infarction (MI), angina pectoris, or coronary artery bypass graft (CABG) within 6 months prior to starting study treatment
    b. QTcF >480 ms at screening, long QT syndrome or family history of unexplained cardiac death
    c. Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block) unless well controlled and clinically addressed in addition to follow-up with cardiologist or agreed by medical monitor

14. Participants with prior malignancy, except:
    a. Participants with history of lower risk MDS treated by supportive care (e.g. growth factors, TGF-beta agents) or untreated are eligible
    b. Participants with history of lower risk MDS who were treated adequately with lenalidomide and then failed are eligible
    c. Participants with history of adequately treated malignancy for which no anticancer systemic therapy (namely chemotherapy, radiotherapy or surgery) is ongoing or required during the course of the study. Participants who are receiving adjuvant therapy such as hormone therapy are eligible.
15. Human immunodeficiency virus (HIV) infection not controlled by standard therapy and/or with known history of opportunistic infection.
16. Active Hepatitis B (HBV) or Hepatitis C (HCV) infection. Participants whose disease is controlled under antiviral therapy should not be excluded. For additional guidance regarding Hepatitis B, please refer to Section 16.4.
17. Other co-morbidity that, in the opinion of the investigator, predisposes the participant to high risk of noncompliance with the protocol.
18. Participants with Myelodysplastic syndrome (MDS) based on 2016 WHO classification (Arber et al 2016) with revised International Prognostic Scoring System (IPSS-R) ≤ 3
19. Sexually active males unwilling to use a condom during intercourse while taking azacitidine or decitabine or INQOVI (oral decitabine) and for 3 months after stopping these drugs. 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. In addition, male participants must not donate sperm for the time period specified above, and their female partners will be instructed to use highly effective contraception.
20. Participant is pregnant or breastfeeding.
21. 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 3 months after the last dose of azacitidine or decitabine or INQOVI (oral decitabine) (or as per their respective local labels, whichever is longer) and 150 days after the last dose of MBG453 (sabatolimab). Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female participants on the study the vasectomized male partner should be the sole partner for that participant.
    - 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 are considered post-menopausal and not of child-bearing potential if they have had over 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least 6 weeks before taking study treatment. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential.

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

6 Treatment

6.1 Study treatment

In this study, the "study treatment" refers to the combination of study drugs: MBG453 (sabatolimab) plus hypomethylating agent (IV/SC/Oral).

The term "investigational drug" refers to the Novartis study drug, MBG453 (sabatolimab). The choice of the HMA (as described in the following sections) will be selected by the investigator as per local standard of care (SOC). After study enrollment and investigator choice for HMA is decided [whether azacitadine (IV or SC) or decitabine (IV or oral)], type of HMA and mode of administration must not be changed during the study course. In case of emergency clinical care during the study course, it will be allowed for patients switching from oral to IV decitabine during inpatient as per investigator decision. Switching from IV to oral decitabine during emergency clinical care requires following the label to complete the IV cycle to reach steady state of decitabine levels.

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.

Table 6-1 Investigational drugs

Investigational Drug (Name and strength)	Dose Administration	Pharmaceutical Dosage Form	Route of Administration	Obtained by
MBG453 (sabatolimab) 400mg/4ml	800mg every 4 weeks at day 8 (For IV and SC HMAs, sabatolimab (MBG453) can be	Solution for infusion	Intravenous use	Sponsor

	administered on a day between days 5-8 as per investigator decision)			

Table 6-2 Study drugs

Study Drug (Name and strength)	Dose Administration	Pharmaceutical Dosage Form	Route of Administration	Obtained by
Decitabine 50mg single vial**	20mg/m2 D1-D5	Lyophilized powder	Intravenous use	Site
Decitabine Oral (INQOVI)	100mg cedazuridine / 35mg decitabine QD D1 to D5	Tablet	Oral	Site
Azacitidine 100 mg single vial**	75mg/m2 D1-D7 or D1 to D5 + D8 & D9	Lyophilized powder	Intravenous or subcutaneous use	Site
**Other locally available dose strengths are acceptable				

Azacitidine and decitabine regimens used in this protocol were selected because they are the most studied regimens and recommended by international treatment guidelines (National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO), Steensma 2018). Azacitidine and decitabine are considered as a Standard of Care in the population enrolled in this study and it should be administered according to standard local clinical practice.

Decitabine should be administered according to local standard clinical practice. A standard dose of decitabine (20 mg/m2) will be given intravenously every day for five consecutive days on Days 1-5 out of a 28 days cycle (see local decitabine US package insert) or 100mg/35mg QD D1 to D5 out of a 28 days cycle if using oral formulation. The food intake requirement for oral formulation should be consistent with approved oral decitabine label, no food should be consumed 2 hours before and 2 hours after each dose of oral decitabine. MBG453 (sabatolimab) infusions will be administered on Day 8 out of a 28 days cycle (For IV and SC HMAs, sabatolimab (MBG453) can be administered on a day between days 5-8 as per investigator decision) (Table 8-1).

Azacitidine should be administered according to local standard clinical practice. A standard dose of azacitidine (75 mg/m2) will be given subcutaneously or intravenously every day for seven consecutive days on Days 1-7 out of a 28 days cycle (see local azacitidine US package insert). In keeping with standard clinical practice, the alternative schedule of 75 mg/m2 for five consecutive days on Days 1-5, followed by a two-day break, then two consecutive days on Days 8-9 will also be permitted (alternative schedule). MBG453 (sabatolimab) infusions will be

administered on Day 8 out of a 28 days cycle (For IV and SC HMAs, sabatolimab (MBG453) can be administered on a day between days 5-8 as per investigator decision) (Table 8-1).
If the alternative schedule is selected for azacitidine by the investigator, azacitidine and MBG453 (sabatolimab) will be given on the same Day 8 (For IV and SC HMAs, sabatolimab (MBG453) can be administered on a day between days 5-8 as per investigator decision).
Azacitidine should be administered first, followed by MBG453 (sabatolimab).
An interval of 1 hour is recommended between the two dose administrations.

MBG453 (sabatolimab) will be administered via IV infusion over 30 minutes. Further instructions for the preparation and administration of MBG453 (sabatolimab) are described in Section 6.7 and in the [CMBG453B1US01 Pharmacy Manual].

6.1.1 Additional study treatments

No other treatment beyond investigational drugs are included in this trial.

6.1.2 Treatment arms/group

Not applicable.

6.1.3 Guidelines for continuation of treatment

The study treatment consists of HMA plus MBG453 (sabatolimab). Planned duration of a cycle is 28 days. Treatment will continue until a protocol-defined reason for discontinuation is met (Section 9).

Per protocol, dose modifications including interruptions for toxicities are permitted (Section 6.5).

6.1.4 Treatment duration

The planned duration of treatment with MBG453 (sabatolimab) is up to 24 months. After the 12 month core phase, patients will have the option to transition to an extra 12 months in the extension phase (based on investigator decision). For patients that will receive treatment in the extension phase, they are allowed to continue treatment with MBG453 and azacitidine/decitibine/INQOVI (oral decitibine), azacitidine/decitibine/INQOVI (oral decitibine) alone, or MBG453 alone.

In addition, all patients who discontinued any study treatments (unless due to progression) may enter the extension phase. In the extension phase, patients who discontinued any study treatment due to reasons other than progression, death, lost to follow-up, or withdrawal of consent (i.e. transplantation, adverse events, etc.) will have hematology assessments, Patient Reported Outcomes (PRO) and response assessments at defined timepoints until documented disease progression, death, lost to follow-up, withdrawal of consent, or end of the extension phase, whichever comes first (Table 8-1). Patients who progress on study (core phase (first 12 months) or extension phase (maximum addition of 12 months)) will enter the post treatment safety follow up period.

Participants who become eligible for hematopoietic stem cell transplant (HSCT) at any time during the course of the study will be discontinued from investigational study treatment

(MBG453 (sabatolimab)). [redacted]

Post treatment follow up is for safety collection and is up to 150 days post core phase or extension phase discontinuation (see Figure 3-1). Survival data will be collected until end of study inclusive of the post treatment follow up duration.

At any time during the study, continuation of treatment beyond progression (excluding transformation to acute leukemia) may be possible in selected participants (Section 6.1.4.1).

Participants may continue azacitidine or decitabine or INQOVI (oral decitabine) alone or MBG453 (sabatolimab) alone if the investigator considers this is in the best interest for the participant. In this case, the participants should continue to conduct the assessments outlined for treatment phase in Table 8-1.

6.1.4.1 Treatment beyond disease progression

Participants with immunotherapy may get clinical benefit despite initial evidence of disease progression. Participants will be allowed to continue the study treatment, (HMA and/or MBG453 (sabatolimab)) beyond disease progression through the extension phase if all four of the following criteria are met:

1. Absence of acute leukemia per WHO 2016 classification (as defined as ≥20% of blasts in bone marrow and/or peripheral blood) (Arber et al 2016)
2. There is a clinical benefit observed per investigator assessment. The clinical benefit at the time of disease progression should consist of :

- Improved or stable ECOG performance status and no cell lineage (neutrophils count, platelets count, hemoglobin) have worsened by >25% as compared to baseline status
- And, at least one of the two following criteria:
  - Improvement or stabilization of cytopenia in at least one cell lineage (neutrophils count, platelets count, hemoglobin) as compared to baseline values, or
  - Reduction of RBC/platelet transfusion needs within the 8 weeks prior to evidence of disease progression as compared to transfusion needs reported prior to enrollment

3. No unacceptable toxicity is reported
4. The participant continues to follow all protocol requirements

In addition, treatment beyond disease progression should not jeopardize critical interventions to treat/prevent severe complications or prevent participants from receiving adequate care.

If the study treatment continues, the participants should continue to perform all assessments for extension phase as per Table 8-1.

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, 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 MBG453 (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 or Grade 4 infusion reaction, the investigational drug should be discontinued.

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 or Grade 4 anaphylactic/anaphylactoid reaction, the investigational drug should be discontinued.

MBG453 (sabatolimab) should be administered in a facility equipped for cardiopulmonary resuscitation. Appropriate resuscitation equipment should be available and a physician should be readily available.

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

Relevant prior and all concomitant medication and non-drug therapies will be collected. Blood transfusions taken within 16 weeks before enrollment and during the course of the study should be recorded in the appropriate case report form (CRF). Transfusion should be collected every 2 months during post-treatment follow-up.

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.

Supportive therapy including prophylactic antibiotic and antifungal treatments, transfusions, will be administered at the discretion of the investigators according to their local standard of care. Transient use of Granulocyte Colony Stimulating Factor (G-CSF) is allowed according to the local standard of care, e.g., in the context of infection or septicemia. Erythropoietin stimulating agents (ESA) and Thrombopoietic agents are prohibited during the study.

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

Regarding the SARS-CoV-2 vaccination:

- 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. Recognizing that multiple vaccines may have various mechanisms of action with different associated potential risks, please reach out to Novartis to discuss specific recommendations related to the use of SARS-CoV-2 vaccines in sabatolimab clinical trials.

- For patients enrolled in Novartis clinical trials who receive a COVID-19 vaccine which is permitted* for use by a local Health Authority, we will capture the vaccine as a concomitant medication (in the respective CRF page), and IRB/EC approval and inclusion in Informed Consent are not required. [*Permitted includes full approval, conditional approval, emergency use authorization, provisional/temporary/interim authorization by Health Authority i.e., outside of a COVID-19 clinical trial to evaluate the effectiveness/safety of a COVID-19 vaccine.] Exceptions may apply if a Health Authority considers the vaccine to be "investigational". As of 08-Dec-2020, there are no known exceptions.
- Although there will be no mandate to vaccinate clinical trial participants against SARS-CoV-2 prior to entry into a trial, patients will be advised to have vaccination against SARS-CoV-2, if available and recommended according to local practice.
- For the patients already in the study, the decision and timing of vaccination for SARS-CoV-2 should be made on a case-by-case basis and at the discretion of the treating physician. In immunosuppressed patients, vaccination failure is a known risk. Vaccination against COVID-19, unless these are live vaccines, is allowed during the study but should not be administered on the same day of study treatment administration as recommended by the ASCO guidelines (Schneider et al 2021).
- No data are yet available on the efficacy and safety of vaccines against SARS-CoV-2 in patients with cancer treated with sabatolimab, including the ideal timing of administration.

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 MBG453 (sabatolimab).

6.2.2 Prohibited medication

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

Additionally, no immunosuppressive medication may be administered while on study drug unless given for the management of immune toxicity.

The use of systemic steroid therapy and other immunosuppressive drugs are not allowed except for the treatment of infusion reaction, immune related adverse events (irAEs), for prophylaxis against imaging contrast dye allergy or replacement-dose steroids in the setting of adrenal

insufficiency or transient exacerbation of other underlying diseases such as chronic obstructive pulmonary disease requiring treatment for ≤ 3 weeks. Systemic corticosteroids required for control of infusion reactions or irAEs must be tapered and be at non-immunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next study administration. If more than 10 mg/day prednisone is used, study drug should be interrupted until the participant receives 10 mg/day or less of prednisone. Topical, inhaled, nasal and ophthalmic steroids are allowed.
The use of live vaccines are not allowed through the duration of the study treatment.
Inactivated vaccines, subunits recombinant, polysaccharide and conjugate vaccines and toxoid vaccines are allowed. Vaccination against COVID-19 is allowed during screening and during the treatment phase, unless theseare live vaccines, but should not be administered on the same day of study treatment administration to avoid potential overlapping adverse events. Prior exposure to cancer vaccines are allowed except if the vaccine was administered within 4 months prior to enrollment. Administration of any inactivated vaccines and any covid-19 vaccines will be documented in the CRFs.

Erythropoietin stimulating agents and Thrombopoietic agents are prohibited during the study. Of note, transient use of Granulocyte Colony Stimulating Factor (G-CSF) is allowed according to the local standard of care, e.g., in the context of infection or septicemia

In addition, prohibited medication related to INQOVI (oral decitabine), decitabine and azacitidine will apply according to local label.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.) that is assigned when the participant is first enrolled for screening and is retained as the primary identifier unless the participant is re-screened. The Participant identifier consists of the Center Number (Center No.), (as assigned by Novartis to the investigative site) with a sequential Participant No. suffixed to it, so that each patient's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the site will use the electronic data capture system to assign the participant the next sequential Participant No.

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 patient fails to be enrolled or start treatment for any reason, the reason will be entered into the appropriate eCRF page. 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 patients.

6.3.2 Treatment assignment, randomization

Not applicable.

6.4 Treatment blinding

Not applicable.

6.5 Dose Modification

Dose escalation is not applicable.

For participants who do not tolerate the protocol-specified dosing schedule, dose modifications consisting in dose interruptions are either recommended or mandated in order to allow participants to continue the study treatment.

Dose modifications for HMA will be done according to local practice and US package insert. Dose modifications for MBG453 (sabatolimab) will be done according to ASCO guidelines about 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 HMA or MDS and its complications.

General guidelines are to follow local practice, US package insert, and ASCO guidelines for HMAs. Further guidance is provided below.

Deviations to mandatory dose interruptions, reductions and/or permanent discontinuations are not allowed.

- **Dose modifications for MBG453 (sabatolimab)** (See Table 6-3 and refer to Brahmer et al 2018)

Administration of MBG453 (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 and the cycle will be shifted accordingly. Dose reductions for MBG453 (sabatolimab) are not allowed; however, longer intervals for administration (Q8W instead of Q4W) are permitted in some clinical situations, as described in Table 6-3.

Overall, for adverse events of potential immune-related etiology (irAE) that do not recover to ≤ Grade 1 or baseline at a dose of immunosuppression of ≤ 10 mg/day prednisone or equivalent (or as indicated in section 6.5.1) within 12 weeks after initiation of immunosuppressive therapy, MBG453 (sabatolimab) must be permanently discontinued.

- **Dose modifications for HMA**

If azacitidine or decitabine or INQOVI (oral decitabine) treatment is deemed by the investigator to possibly have contributed to an observed adverse event, the dose or schedule of hypomethylating agent treatment may be modified within a cycle and/or for subsequent cycles or temporary/permanent interruptions of HMA treatment may be decided by the investigator according to local practice and/or the US package insert guiding azacitidine or decitabine or INQOVI (oral decitabine) use.

- **Permanent discontinuation of MBG453 (sabatolimab) and HMA**

If the study treatment is interrupted for toxicities and the start of the subsequent study treatment cycle is delayed for more than 56 consecutive days (i.e. 2 planned consecutive cycles of study

treatment for both, HMA and MBG453 (sabatolimab)) the participant should be discontinued from study treatment.

- **Permanent discontinuation of only one component MBG453 (sabatolimab) or HMA**

If **one component only** of the study treatment (HMA OR MBG453 (sabatolimab)) is discontinued for toxicities, then the treatment may continue with the other component of study treatment alone (MBG453 (sabatolimab) or HMA alone) as long as the participant benefits per investigator's judgement.

All dose changes must be recorded on the appropriate CRF.

Criteria for re-initiation of study drug MBG453 (sabatolimab) for adverse drug reactions

Table 6-3 Criteria for re-initiation of study drug MBG453 (sabatolimab) for adverse drug reactions

Worst Toxicity CTCAE v5.0 Grade	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 adequate pre-medication, then discontinue treatment
Grade 3 or 4	Discontinue MBG453 (sabatolimab)
For toxicities 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	
Grade 1	No change. Continue MBG453 (sabatolimab) at the same dose (800 mg) and schedule (Q4W)
Grade 2 or Grade 3 ≤7 days	Delay MBG453 (sabatolimab) until toxicity resolved to≤ Grade 1 or baseline. Then resume at the same dose (800 mg) and schedule (Q4W)
Grade 3 lasting >7 days but <21 days	Delay MBG453 (sabatolimab) until toxicity resolved to ≤Grade 1 or baseline. Then resume at the same dose (800 mg) but with a longer treatment interval (Q8W). Return to the initial treatment interval (Q4W) may be possible but only after discussion and agreement with Novartis Medical Lead
Grade 3 lasting ≥21 days Or Grade 4	Discontinue MBG453 (sabatolimab)
General guideline for non-hematologic, non-immune-related toxicities that are clinically significant** and at least possibly attributable to the investigational drug. This guideline does not apply for toxicities attributable to HMA (decitabine or INQOVI (oral decitabine) or azacitidine) or the underlying MDS including its complications.	

Grade 1	No change. Continue MBG453 (sabatolimab) at the same dose (800 mg) and schedule (Q4W)
Grade 2 or Grade 3 ≤7 days	Delay MBG453 (sabatolimab) until toxicity resolved to ≤Grade 1 or baseline. Then resume at the same dose (800 mg) and schedule (Q4W)
Grade 3 >7 days	Delay MBG453 (sabatolimab) until toxicity resolved to ≤Grade 1 or baseline. Then resume at the same dose (800 mg) but with a longer treatment interval (Q8W). Return to the initial treatment interval (Q4W) may be possible but only after discussion and agreement with Novartis Medical Lead
Grade 4	Discontinue MBG453 (sabatolimab)
All dose modifications should be based on the available information and worst preceding toxicity. * Infusion related reaction or allergic reaction/anaphylaxis. See section 6.2.1 for instructions regarding prophylaxis. ** Per investigator judgement.	

6.5.1 Follow-up for toxicities

Patients 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.

In addition to the instructions provided in this section, please refer to Section 16.2 (Appendix 2) for further guidance on liver events, laboratory trigger definitions and follow-up requirements. For guidance on renal alert criteria, actions and events follow up, please refer to Section 16.3 (Appendix 3).

All patients must be followed up for AEs for 30 days following the last dose of azacitidine or decitabine or INQOVI (oral decitabine), or 150 days following the last dose of MBG453 (sabatolimab), whichever is later.

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 unlikely. Serologic, histologic and immunological assessments should be performed as deemed appropriate by the Investigator, to verify the immune related nature of the AE. An empiric trial of corticosteroids may also contribute to understanding the etiology of a potential irAE. All patients with signs or symptoms of irAEs should be monitored and managed following the ASCO Guidelines for the

management of immune-related adverse events in participants treated with immune checkpoint inhibitor therapy.

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

Tumor lysis syndrome

Tumor lysis syndrome (TLS) is a clinical entity frequently observed in hematological malignancies resulting from massive tumor cells lysis. It is characterized by a constellation of metabolic abnormalities caused by the massive and abrupt release of cellular components (including nucleic acids, proteins, and electrolytes) into the systemic circulation after the rapid lysis of malignant cells (Coiffier et al 2008). TLS is not frequent in MDS and no cases of TLS has been reported in the ongoing CPDR001X2105 for MDS participants receiving MBG453 (sabatolimab) in combination with decitabine.

During this study, participants should be closely monitored (including relevant laboratory tests) for signs and symptoms of TLS before initiation and during a treatment cycle. To minimize risk of TLS, participants with elevated uric acid or high tumor burden should receive allopurinol, or an alternative prophylaxis, prior to study treatment. Events should be managed according to local guidelines.

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

- Before initiation of a treatment cycle:
  - Prophylactic allopurinol, or a non-allopurinol alternative (e.g., febuxostat), and increased oral/ IV hydration prior to treatment should be given in participants with elevated uric acid or high tumor burden
  - Prompt supportive care in case of acute TLS (IV fluids and treatment with rasburicase as clinically indicated, when uric acid continues to rise despite allopurinol/febuxostat and fluids)
- During a treatment cycle:
  - Frequent monitoring of the following laboratory tests (per assessment cycle and as clinically indicated): potassium, phosphorus, calcium, creatinine, and uric acid
  - Encourage oral hydration

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

Laboratory tumor lysis syndrome

- Defined as two or more of the following values within 3 days before or in the days following initiation of a treatment cycle:
  - Uric acid $\geq$ 8 mg/dL or 25% increase from baseline
  - Potassium $\geq$ 6 mEq/L or 25% increase from baseline

- Phosphorus ≥ 6.5 mg/dL (children) or ≥ 4.5 mg/dL (adults) or 25% increase from baseline
- Calcium ≤ 7 mg/dL or 25% decrease from baseline

- Regimen:
  - If none or one of the laboratory values above is abnormal, continue to manage with allopurinol or a non-allopurinol alternative (e.g., febuxostat) and oral fluids. If uric acid remains elevated, consider IV fluids, treatment with rasburicase, and hospital monitoring.
  - Laboratory TLS should be managed with IV fluids, laboratory blood tests every 6 to 8 hours and inpatient care. Cardiac monitoring and treatment with rasburicase should be considered if uric acid remains elevated.

Clinical tumor lysis syndrome

- Defined as the presence of laboratory TLS and ≥ 1 of the following criteria that cannot be explained by other causes:
  - Serum creatinine ≥ 1.5 times the upper limit of the age-adjusted normal range
  - Symptomatic hypocalcemia
  - Cardiac arrhythmia
  - Regimen: Clinical TLS should be managed with IV fluids, laboratory blood tests every 6 to 8 hours, cardiac monitoring, and treatment with rasburicase/allopurinol/febuxostat and inpatient care (consider intensive care unit (ICU)).

Patients who have been treated for TLS with favorable outcome (defined as return to within 10% of baseline value or within limit of normal of relevant laboratory parameters) may re-start study treatment upon discussion between the sponsor and the investigator.

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

Guidelines for follow-up on potential DILI cases are described in Table 6-4 and Table 6-5.

Table 6-4 Follow-up of abnormal liver chemistry results

ALT	TBL	Liver Symptoms	Action
ALT increase without bilirubin increase:			
If normal at baseline: ALT >3 x 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 ALT, AST, ALP, GGT, TBL, INR, albumin and CK in 48- 72 hours (GLDH is recommended as well) - Follow-up for symptoms
If normal at baseline: ALT >5 x ULN for more than two weeks	Normal For participants with	None	- Interrupt investigational drug

If elevated at baseline: ALT >3 x baseline or >300 U/L (whichever occurs first) for more than two weeks	Gilbert's syndrome: No change in baseline TBL		- Measure ALT, AST, ALP, GGT, TBL, INR, albumin and CK in 48- 72 hours (GLDH is recommended as well). - Follow-up for symptoms. - Initiate close monitoring and workup for competing etiologies. - Investigational drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
If normal at baseline: ALT >8 x	Normal	None	
ALT increase with bilirubin increase:			
If normal at baseline: ALT >3 x	TBL >2 x ULN (or INR >1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
If elevated at baseline: ALT >2 x baseline or >200 U/L (whichever occurs first)			
If normal at baseline: ALT >3 x ULN	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	
If elevated at baseline: ALT >2 x baseline or >200 U/L (whichever occurs first)			

Table 6-5 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 Liver Function Tests (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 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.
2. Review of concomitant medications, including nonprescription medications and herbal and dietary supplement preparations, alcohol use, recreational drug use, special diets, and chemicals exposed to within one month of the onset of the liver injury.

3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. [redacted]
5. Additional testing for other hepatotropic viral infection (Cytomegalovirus, Epstein–Barr virus or Herpes-simplex virus), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

6.5.1.2 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). 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.
- Contact Novartis Medical Lead in case QTcF >500 ms or QTcF prolongation >60 ms from baseline.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

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

MBG453 (sabatolimab) will be administered to the patient by the study site staff. Decitabine or azacitidine (IV/SC) will be administered per site regulations. This may include administration by study site staff, or local administration at another hospital or through home administration by qualified site staff, or by trained non-study personnel. Compliance will be assured by administration of the study treatment under the supervision of investigator or his/her designee.

All dosages for MBG453 (sabatolimab) well as HMAs prescribed to the participant and all dose changes during the study must be recorded on the corresponding Dosage Administration Record eCRF.

6.6.2 Emergency breaking of assigned treatment code

Not applicable

6.7 Preparation and dispensation

MBG453 (sabatolimab)

MBG453 (sabatolimab) (800 mg) will be administered IV. Further instructions for the preparation and dispensation of MBG453 (sabatolimab) are described in the Pharmacy Manual.

All dosages for MBG453 (sabatolimab) prescribed to the participant and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

Decitabine (IV and INQOVI (oral decitabine))

For details on preparation refer to the US package insert instructions and/or IV decitabine or INQOVI (oral decitabine) package insert, if the drug is commercially available. All dosages for decitabine or INQOVI (oral decitabine) prescribed to the participant and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

Azacitidine

For details on preparation refer to the US package insert instructions and/or azacitidine package insert, if the drug is commercially available. All dosages for azacitidine prescribed to the participant and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

Public Health emergency

As per section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of IMP directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of X-months supply. In this case, regular phone calls or virtual contacts (every Y weeks or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, drug accountability, investigation of any adverse events, ensuring participants continue to benefit from treatment and discussion of the participant´s health status until the participants can resume visits at the study site.

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 treatments 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.

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 field 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.

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 (IRB) / Institutional Ethics Committee (IEC) approved informed consent.

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

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

The date when a participant’s Informed Consent was actually obtained will be captured in their CRFs.

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

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

notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The study includes the option for the subjects to continue MBG453 alone. The study also includes the option for the subjects to continue treatment with MBG453 and azacitidine/decitibine/INQOVI (oral decitibine), azacitidine/decitibine/INQOVI (oral decitibine) alone, MBG453 alone beyond progression in selected subjects without acute leukemia (see Section 6.1.4.1).

In both options (continuation of MBG453 alone, or continuation of treatment beyond progression), this will require informed consent before treatment continuation if the subject agrees to participate. It is required as part of this protocol that the investigator presents these options to the subjects, as permitted by local governing regulations. The process for obtaining consent should be the same as described above for the main informed consent.

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements for the duration of the study and 150 days after the last dose of MBG453 (sabatolimab).

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

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

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

[redacted]

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

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

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

8 Visit schedule and assessments

Assessment schedules (Table 8-1) lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

No eCRF will be used as a source document.

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). Bone marrow aspirate (BMA) or biopsy performed prior to signing informed consent but within 28 days from the informed consent, may be used. [redacted] Instead, a viable cryopreserved BMA sample collected prior to informed consent signature (but within 28 days from the informed consent) should be provided, if available.

If the hematology and chemistry laboratory tests are performed within 7 days before enrollment, it is not required to perform them again on C1D1.

During the course of the study visits, test and/or procedures should occur on schedule whenever possible. During the core phase and extension phase, a visit window of +/- 7 days is allowed. During the post- treatment follow up phase a visit window of +/-14 days is allowed.

In case the infusion of MBG453 (sabatolimab), azacitidine or decitabine cannot be administered at the scheduled visit, it has to be administered as soon as possible. Every effort should be made on C1D1 for the drug to be administered on the same day as enrollment. A visit window of +7 days is allowed for treatment administration for reason other than toxicities. [redacted]

Participants who discontinue the study treatment for any reason should be scheduled for an end of treatment (EOT) visit within 7 days from the date that the participant discontinued from treatment, at which time all of the assessments listed for the EOT visit will be performed (if bone marrow aspirate or biopsy was performed within 14 days from the EOT visit, the assessment does not have to be repeated).

All participants receiving the study treatment must have safety evaluations for 30 days after the last dose of decitabine or INQOVI (oral decitabine) or azacitidine, or 150 days after the last dose of MBG453 (sabatolimab), whichever occurs later. After the safety follow-up on site visit on Day 30, participants will be followed via telephone call for the Day 90 and Day 150 (or onsite visit if patient happens to be visiting the site).

For post-treatment follow-up and survival information, please refer to Section 9.1.6.

As per section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowed by local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

Table 8-1 Assessment Schedule

Period	**Scr**	**Core**																**EOT[7]**
Cycle		**Cycle 1 (28d)**		**Cycle 2 (28d)**		**Cycle 3 (28d)**		**Cycle 4 (28d)**		**Cycle 5 (28d)**		**Cycle 6 (28d)**		**Cycle 7 (28d)**		**Cycle 8 (and beyond until Cycle 13) (28d)[7]**		
Visit Name	**Screeni**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15 (17, 19, 21**	**16 (18, 20, 22 +)**	**EOT[7]**
Days	**-28 to -1**	**D1**	**D8[1]**	**D1**	**D8[1]**	**D1**	**D8[1]**	**D1**	**D8[1]**	**D1**	**D8[1]**	**D1**	**D8[1]**	**D1**	**D8[1]**	**D1**	**D8[1]**	**-**
Informed consent	X																	
Demography	X																	
Inclusion / Exclusion criteria	X																	
Medical history/current medical conditions	X																	
Disease History	X																	
Prior antineoplastic therapies	X																	
Prior medications, surgery and medical procedures (including blood transfusions requirement)	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																	

Period	**Scr**	**Core**																**EOT**[7]
Cycle		**Cycle 1 (28d)**		**Cycle 2 (28d)**		**Cycle 3 (28d)**		**Cycle 4 (28d)**		**Cycle 5 (28d)**		**Cycle 6 (28d)**		**Cycle 7 (28d)**		**Cycle 8 (and beyond until Cycle 13) (28d)** [7]		
Visit Name	**Screeni**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15 (17, 19, 21 +)**	**16 (18, 20, 22**	**EOT**[7]
Days	**-28 to -1**	**D1**	**D8**[1]	**D1**	**D8**[1]	**D1**	**D8**[1]	**D1**	**D8**[1]	**D1**	**D8**[1]	**D1**	**D8**[1]	**D1**	**D8**[1]	**D1**	**D8**[1]	**-**
BSA (use height from screening)		X		X		X		X		X		X		X		X		
Body Weight	X	X		X		X		X		X		X		X		X		X
ECOG PS	X	X		X		X		X		X		X		X		X		X
12-Lead ECG (triplicates)	S	If clinically indicated																S
Hematology	X[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Chemistry	X[2]	X		X		X		X		X		X		X		On cycle 9, 11, and 13		X
Coagulation	X	X		X		X		X		X		X		X		On cycle 9, 11, and 13		X
Thyroid function	X			X						X						On cycle 8 and 11		X

[redacted]

Period	**Scree**	**Core**																**EOT7**
Cycle		**Cycle 1 (28d)**		**Cycle 2 (28d)**		**Cycle 3 (28d)**		**Cycle 4 (28d)**		**Cycle 5 (28d)**		**Cycle 6 (28d)**		**Cycle 7 (28d)**		**Cycle 8 (and beyond until Cycle 13) (28d)** 7		
Visit Name	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15 (17, 19, 21**	**16 (18, 20, 22 +)**	**EOT7**
Days	**-28 to -1**	**D1**	**D81**	**D1**	**D81**	**D1**	**D81**	**D1**	**D81**	**D1**	**D81**	**D1**	**D81**	**D1**	**D81**	**D1**	**D81**	**-**
Virology hepatitis B and C	S	If clinically indicated																
HIV serology (only if required per local regulation)	S																	
Serum Pregnancy Test (only women with child-bearing potential)	S	S																S
Urine Pregnancy Test OR Serum Pregnancy Test (only women with child-bearing potential)				S		S		S		S		S		S		S		
Urinalysis dipstick and sediment	S	If clinically indicated																
Efficacy - Bone marrow aspirate and/or biopsy5	X3							X						X		On cycle 10 and 13		X

Period	**Screening**	**Core**																**EOT**[7]
Cycle		**Cycle 1 (28d)**		**Cycle 2 (28d)**		**Cycle 3 (28d)**		**Cycle 4 (28d)**		**Cycle 5 (28d)**		**Cycle 6 (28d)**		**Cycle 7 (28d)**		**Cycle 8 (and beyond until Cycle 13) (28d)**[7]		
Visit Name	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15 (17, 19, 21**	**16 (18, 20, 22 +)**	**EOT**[7]
Days	**-28 to -1**	**D1**	**D8**[1]	**D 1**	**D8**[1]	**D1**	**D8**[1]	**D1**	**D8**[1]	**D1**	**D8**[1]	**D1**	**D8**[1]	**D1**	**D8**[1]	**D1**	**D8**[1]	**-**
Efficacy - Peripheral blood collection[5]	X							X						X		On cycle 10, 13 and if clinically indicated		X
Cytogenetics	X																	
Response assessment														X		On cycle 13 and if clinically indicated		X
[redacted]																		

Period	Screening	Core																EOT[7]
Cycle		Cycle 1 (28d)		Cycle 2 (28d)		Cycle 3 (28d)		Cycle 4 (28d)		Cycle 5 (28d)		Cycle 6 (28d)		Cycle 7 (28d)		Cycle 8 (and beyond until Cycle 13) (28d)[7]		
Visit Name	Screening	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15 (17, 19, 21 +)	16 (18, 20, 22 +)	EOT[7]
Days	-28 to -1	D1	D8[1]	D1	D8[1]	D1	D8[1]	D1	D8[1]	D1	D8[1]	D1	D8[1]	D1	D8[1]	D1	D8[1]	-
[redacted]																		

Period	**Screening**	**Core**																**EOT**[7]
Cycle		**Cycle 1 (28d)**		**Cycle 2 (28d)**		**Cycle 3 (28d)**		**Cycle 4 (28d)**		**Cycle 5 (28d)**		**Cycle 6 (28d)**		**Cycle 7 (28d)**		**Cycle 8 (and beyond until Cycle 13) (28d)** [7]		
Visit Name	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15 (17, 19, 21 +)**	**16 (18, 20, 22 +)**	**EOT**[7]
Days	**-28 to -1**	**D1**	**D8**[1]	**D1**	**D8**[1]	**D1**	**D8**[1]	**D1**	**D8**[1]	**D1**	**D8**[1]	**D1**	**D8**[1]	**D1**	**D8**[1]	**D1**	**D8**[1]	**-**
[redacted]																		
Azacitidine infusion or SC		If chosen: on Days 1- 7 of each cycle OR on Days 1-5 and then on Day 8 and Day 9: IV or SC 75mg/m2																
Decitabine infusion		If chosen: on Days 1-5 of each cycle																
Oral decitabine/ cedazuridine		If chosen: on Days 1-5 of each cycle																
Infusion MBG453 (sabatolimab)			X_1		X_1		X_1		X_1		X_1		X_1		X_1		X_1	
Adverse Events	X	Continuous																

Period	**Screening**	**Core**																**EOT**[7]
Cycle		**Cycle 1 (28d)**		**Cycle 2 (28d)**		**Cycle 3 (28d)**		**Cycle 4 (28d)**		**Cycle 5 (28d)**		**Cycle 6 (28d)**		**Cycle 7 (28d)**		**Cycle 8 (and beyond until Cycle 13) (28d)** [7]		
Visit Name	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15 (17, 19, 21 +)**	**16 (18, 20, 22 +)**	**EOT**[7]
Days	**-28 to -1**	**D1**	**D8**[1]	**D1**	**D8**[1]	**D1**	**D8**[1]	**D1**	**D8**[1]	**D1**	**D8**[1]	**D1**	**D8**[1]	**D1**	**D8**[1]	**D1**	**D8**[1]	**-**
Concomitant medications and medical procedures (including blood transfusions requirement)	X	Continuous																
Antineoplastic therapies, HSCT and transfusions	X																	
Disposition	X																	X
Survival Follow up																		

Period	**Extension**												
Cycle	**Cycle 1 (28d)**	**Cycle 2 (28d)**	**Cycle 3 (28d)**	**Cycle 4 (28d)**	**Cycle 5 (28d)**	**Cycle 6 (28d)**	**Cycle 7 (28d)**	**Cycle 8 (28d)**	**Cycle 9 (28d)**	**Cycle 10 (28d)**	**Cycle 11 (28d)**	**Cycle 12 (28d)**	**Cycle 13 (28d)**
Visit Name	**Ext 1**	**Ext 2**	**Ext 3**	**Ext 4**	**Ext 5**	**Ext 6**	**Ext 7**	**Ext 8**	**Ext 9**	**Ext 10**	**Ext 11**	**Ext 12**	**Ext 13**
Hematology	X	If clinically indicated		X	If clinically indicated		X	If clinically indicated		X	If clinically indicated		X
Chemistry	If clinically indicated												
Coagulation	If clinically indicated												
Thyroid function	If clinically indicated												
[redacted]													
Virology hepatitis B and C	If clinically indicated												
HIV serology (only if required per local regulation)	If clinically indicated												
Urine Pregnancy Test OR Serum Pregnancy Test (only women with child-bearing potential)	S	S	S	S	S	S	S	S	S	S	S	S	S
Urinalysis dipstick and sediment	If clinically indicated												

Period	**Extension**												
Cycle	**Cycle 1 (28d)**	**Cycle 2 (28d)**	**Cycle 3 (28d)**	**Cycle 4 (28d)**	**Cycle 5 (28d)**	**Cycle 6 (28d)**	**Cycle 7 (28d)**	**Cycle 8 (28d)**	**Cycle 9 (28d)**	**Cycle 10 (28d)**	**Cycle 11 (28d)**	**Cycle 12 (28d)**	**Cycle 13 (28d)**
Visit Name	**Ext 1**	**Ext 2**	**Ext 3**	**Ext 4**	**Ext 5**	**Ext 6**	**Ext 7**	**Ext 8**	**Ext 9**	**Ext 10**	**Ext 11**	**Ext 12**	**Ext 13**
Efficacy - Bone marrow aspirate and/or biopsy[5]	X	If clinically indicated					X	If clinically indicated					X
Efficacy - Peripheral blood collection[5]	X	If clinically indicated					X	If clinically indicated					X
Response assessment	If clinically indicated (for example if progression or relapse is suspected)												
[redacted]													
Azacitidine infusion or SC	If chosen and continuing treatment: on Days 1- 7 of each cycle OR on Days 1-5 and then on Day 8 and Day 9: IV or SC 75mg/m2												

Period	**Extension**												
Cycle	**Cycle 1 (28d)**	**Cycle 2 (28d)**	**Cycle 3 (28d)**	**Cycle 4 (28d)**	**Cycle 5 (28d)**	**Cycle 6 (28d)**	**Cycle 7 (28d)**	**Cycle 8 (28d)**	**Cycle 9 (28d)**	**Cycle 10 (28d)**	**Cycle 11 (28d)**	**Cycle 12 (28d)**	**Cycle 13 (28d)**
Visit Name	**Ext 1**	**Ext 2**	**Ext 3**	**Ext 4**	**Ext 5**	**Ext 6**	**Ext 7**	**Ext 8**	**Ext 9**	**Ext 10**	**Ext 11**	**Ext 12**	**Ext 13**
Decitabine infusion	If chosen and continuing treatment: on Days 1-5 of each cycle												
Oral decitabine/cedazuridine	If chosen and continuing treatment: on Days 1-5 of each cycle												
Infusion Drug Dispensation MBG453 (sabatolimab)[8]	If continuing treatment : on D8 of every cycle												
Adverse Events[8]	Continuous												
Concomitant medications and medical procedures (including blood transfusions requirement)	Continuous												
Antineoplastic therapies, HSCT and transfusions since discontinuation of study treatment[8]	[redacted]												
Disposition													X
Survival Follow up	X						X						X

Period	**Post-treatment Safety FU**	
Cycle		
Visit Name	**D30**	**D150 and beyond**
Days	**-**	**-**
[redacted]		
Serum Pregnancy Test (only women with child-bearing potential)		S (D150 only)
Urine Pregnancy Test OR Serum Pregnancy Test (only women with child-bearing potential)	S (D30, D60, D90, D120 after the last dose of MBG453 (sabatolimab))	
Adverse Events[9]	Continuous until D30 or D150	
Concomitant medications and medical procedures (including blood transfusions requirement)	Continuous	
Antineoplastic therapies, HSCT and transfusions since discontinuation of study treatment	Continuous	
Survival Follow up	Every 6 cycles	

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. For hospital administered HMAs (IV and SC – decitabine 20mg/m2 D1-D5; or azacitadine75mg/m2 D1-D7 or D1 to D5 + D8 & D9), for flexibility of administration of the investigational therapy (sabatolimab) can be administered on any day from D5-D8 based on investigator/patient decision. Currently no data is available on administration of sabatolimab on day 5, 6 or 7. Further data will be collected and evaluated through this study. Based on prior trials change of day of administration and frequency [every two weeks vs. every four weeks] within the cycle of MBG53 may not have additional [redacted] safety concerns.
2. If the hematology and chemistry laboratory tests are performed within 7 days before enrollment, it is not required to perform them again on C1D1.
3. If bone marrow results are available within 28 days prior to informed consent, the procedure does not have to be repeated at screening, the results can be used for diagnosis and baseline. Bone marrow aspirate (BMA) or biopsy performed prior to signing informed consent but within 28 days from the informed consent, may be used. [redacted] Instead, a viable cryopreserved BMA sample collected prior to informed consent signature (but within 28 days from the informed consent) should be provided, if available.
4. [redacted]
5. Bone marrow aspirate and/or biopsy and peripheral blood samples for efficacy assessments should be performed at screening and pre-dose during treatment period (C4D1, C7D1, C10D1, C13D1), aand when clinically indicated at any time during the study
6. Exploratory analysis at Garcia-Manero et al EHA 2020 revealed that patient treated with anti-TIM3 antibody MBG453 (sabatolimab) in combination with HMA for MDS and AML can successfully proceed to allogenic stem cell transplant. To date there are limited toxicity for GVHD. Further data is required.
7. Patient can enter extension phase per investigator decision.
8. To be collected only for patients continuing MBG453 (sabatolimab) treatment. See section 10.1.1.
9. Post treatment safety follow-up monitoring for adverse events (AEs) for 30 days following the last dose of azacitidine or decitabine or INQOVI (oral decitabine), or 150 days following the last dose of MBG453 (sabatolimab), whichever is later. See section 10.1.1.

8.1 Screening

Screening

All participants must provide signed ICFs prior to performing any study specific procedures. Participants will be evaluated against all study inclusion and exclusion criteria.

After signing the study ICFs, screening assessments should be completed within 28 days prior to enrollment (Table 8-1). A patient who has a laboratory tests result(s) that does not satisfy the entrance criteria may have the test(s) repeated. These test(s) may be repeated as soon as the investigator believes the re- test result(s) is/are likely to be within the acceptable range to satisfy the entrance criteria, but may be completed within approximately 3 weeks of the original screening visit date. In this case, the Participant will not be required to sign another ICF, and the original participant ID number assigned by the investigator will be used. In the event that the laboratory test(s) cannot be performed within 3 weeks of the original screening visit, or the re-test(s) do not meet the entrance criteria, or other eligibility criteria have changed and are not met anymore, the patient is considered a screen failure, and must be discontinued from the study.

A new ICF will need to be signed if the investigator chooses to re-screen the patient after a patient has screen failed, and the Participant ID number will change. All required screening activities must be performed when the patient is re-screened for participation in the study. An individual patient may only be re-screened once for the study. Once the number of patients screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In this case, the patients who screen failed will not be permitted to re-screen. Bone marrow and peripheral blood pathology specimens (i.e. bone marrow slides, bone marrow biopsy block if applicable, peripheral blood samples) prepared locally for establishing the MDS diagnosis at the time of screening, should be sent to the Novartis designated central laboratory for storage. A copy of the corresponding pathology reports should be collected and sent to the Novartis designated central laboratory for storage. Central morphology review of the pathology specimens may be performed, if deemed necessary.

8.1.1 Eligibility screening

Participant eligibility will be checked once all screening procedures are completed.

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 enrollment will be considered a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form. 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 SAE section for reporting details, Section 10.1.3).

8.2 Participant demographics/other baseline characteristics

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

- Demography including date of birth, sex, predominant race and ethnicity (where permitted).
- Height and weight (see Table 8-1).
- Medical history (e.g., important medical, surgical, and allergic conditions from the patient's medical history which could have an impact on the patient's evaluation) / current medical conditions (e.g., all relevant current medical conditions which are present at the time of signing informed consent). Ongoing medical conditions, symptoms and diseases which are recorded on the Medical History eCRF must include the toxicity grade when applicable.
- Disease history (MDS), including date of diagnosis, confirmation of MDS diagnosis, IPSS-R risk classification for MDS participants at time of screening, prior antineoplastic therapies. IPSS-R risk score for MDS participants should be calculated based on the hematology values obtained at screening.
- All prior and concomitant medications and medical procedures
- Blood transfusion **administered within 16 weeks** prior to enrollment

Other assessments will be completed to determine eligibility into the study as reported in Table 8-1.

Assessments to be performed at screening include:

- 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, chemistry, coagulation, urinalysis, serum pregnancy test for women of child-bearing potential, thyroid function, [redacted] HIV serology (only if required per local regulation). If multiple laboratory tests were performed during screening to confirm eligibility, the lab values closest to enrollment should be used (last available values during screening).
- Cardiovascular assessments (i.e., triplicate 12-lead ECG)
- [redacted]
- Bone marrow biopsy or aspirate will be performed locally to establish diagnosis (If a bone marrow aspirate or biopsy was conducted during the regular work-up of the participant and falls within 28 days prior to enrollment; although prior to signing main study ICF it may be considered as the baseline assessment for the study).
- Cytogenetics will be performed locally as per local standard
- Patient reported outcomes
- [redacted]
- Adverse events

- Blood should be collected for phenotypic and molecular assessments

Subject race and 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.

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

8.3 Efficacy

Efficacy assessments will be performed according to the IWG and WHO criteria for MDS (Cheson et al 2000, Cheson et al 2006, Arber et al 2016, Platzbecker et al 2018). Response criteria in MDS are described in Table 8-2. Investigators will assess locally at their site and document response/progression at each time point as per the visit schedule. For efficacy analyses, baseline is defined as the last non-missing assessment on or before the date of enrollment.

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

Table 8-2 Modified response classification per IWG criteria in MDS

(Platzbecker et al 2018, Cheson et al 2006, Cheson et al 2000)

Response category	Definition[#]
Complete remission (CR)	**Bone marrow:** ≤ 5% blasts with normal maturation of all cell lineages. (Note: Persistence of dysplasia will be noted but does not preclude achievement of complete remission [CR]) **Peripheral blood** 1. Hgb ≥ 10 g/dL AND 2. Platelets ≥ $100*10^9$/L AND 3. Neutrophils ≥ $1.0*10^9$/L AND 4. Blasts 0% *Note: the participant must not receive RBC or platelet transfusions, myeloid growth factor within 2 weeks before this disease assessment*
marrow Complete remission (mCR)	**Bone marrow:** ≤ 5% blasts and blast count decrease by ≥ 50% compared to baseline **Peripheral blood/transfusion:** Marrow CR may be achieved with or without improved blood counts or with or without transfusions

Partial remission (PR)	**All CR criteria except** **Bone marrow:** ≥ 50% decrease from baseline in blasts in bone marrow AND blast count in bone marrow >5%
Stable Disease (SD)	Failure to achieve at least PR, but no evidence of progression for >8 weeks
Relapse from CR	**Only in participants with a CR:** **At least 1 of the following criteria is met:** **[In absence of another explanation not due to MDS, such as acute infection, bleeding, hemolysis, etc. Note that observation of peripheral blasts is not a sufficient criterion for relapse. However in that case, a bone marrow examination should be made to determine whether relapse has occurred.]** 1. Return to baseline bone marrow blast percentage 2. Decrease of ≥ 50% from maximum remission/response*** levels in neutrophils AND neutrophils $<1.0*10^9$/L. Note: neutrophils counts during periods of active infection will not be considered in determining the maximum 3. Decrease of ≥ 50% from maximum remission/response*** levels in platelets AND platelets $<100*10^9$/L 4. Decrease from maximum remission/response*** levels in Hgb concentration by ≥1.5g/dL AND Hgb <10 g/dL **5.** Becoming transfusion dependent**

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

Modified Hematological Improvement per IWG-MDS criteria in MDS (Cheson et al 2006)	
HI category	**Definition# (HI must last at least 8 weeks)**
Erythroid response (HI-E) **(pretreatment*, <11 g/dL)**	1. Hgb increase from baseline by ≥1.5 g/dL, in at least 2 consecutive Hgb measurements and maintained over at least 8 weeks 2. Relevant reduction from baseline of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pre-treatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hgb of <9 g/dL pre-treatment will count in the RBC transfusion response evaluation.
Platelet response (HI-P) **(pretreatment*, <100 x 10^9/L)**	1. Absolute increase from baseline of ≥ 30 x 10^9/L for participants starting with >20 x 10^9/L platelets 2. Increase from baseline from <20 x10^9/L to >20 x10^9/L and by at least

Neutrophil response (HI-N) (pretreatment*, <1.0 x 10^9/L)	At least 100% increase and an absolute increase from baseline of >0.5 x 10^9/L

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

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

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

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

Transfusions Status Definitions for RBC/platelets

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

Transfusion dependence:

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

Transfusion independence:

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

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

Bone marrow aspirate or biopsy and peripheral blood will be collected per Table 8-1 for assessment of disease. The bone marrow and peripheral blood pathology specimens (i.e. bone marrow aspirate slides, bone marrow biopsy block if applicable, peripheral blood samples) prepared locally for the disease response assessment, should be sent to the Novartis designated central laboratory for storage. This includes specimens taken during the regular work-up of the subject and used as baseline assessment for the study as mentioned in Section 8-2. A copy of the corresponding pathology reports should be collected and sent to the Novartis designated central laboratory for storage. Central morphology review of the pathology specimens may be performed, if deemed necessary. All enrolled participants has to be followed for efficacy, regardless whether treatment received or not. Bone marrow assessments will be performed at screening and pre-dose during treatment period at C4D1, C7D1, C10D1, C13D1, and EOT and hematology assessments will be performed at screening, D1 and D8 of each cycle until end of treatment and if clinically indicated at any time during the study. Screening bone marrow aspirates or biopsies (BMA/BMB) must be collected within 28 days of informed consent. If a participant's screening BMA/BMB was collected >28 days before informed consent, then the participant must agree to have a repeat BMA/BMB performed. Clinical suspicion of relapse or disease progression at any time after enrollment will require a disease evaluation promptly,

rather than waiting for the next scheduled assessment. In case of an unscheduled or delayed disease evaluation for any reason, subsequent assessments should be performed according to the original planned schedule.

More frequent efficacy assessments may be performed at the investigator's discretion, if medically indicated, and recorded as an unscheduled visit in the eCRFs.

Extension phase

Patients completing core phase of 12 months and requiring continuation of study treatment (by investigator decision) beyond 12 months will enter the extension phase. For patients that will receive treatment in the extension phase, they are allowed to continue treatment with MBG453 and azacitidine/decitibine/INQOVI (oral decitibine), azacitidine/decitibine/INQOVI (oral decitibine) alone, or MBG453 alone.

Additionally, for participants who discontinue any study treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent, will enter extension phase.

Efficacy assessments (hematology and bone marrow aspirate/biopsy) should follow Table 8-1. Response assessments must continue to be performed every 3 cycles as per hematology assessment and at least every 6 cycles as per bone marrow assessment or as clinically indicated until documented disease progression/relapse (per IWG criteria Table 8-2), death, lost to follow-up, or withdrawal of consent.

8.3.1 Appropriateness of efficacy assessments

Not applicable.

8.4 Safety

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

For safety evaluations, baseline is defined as assessments done on C1D1 prior to the first dose of study treatment. For assessment which are not done at C1D1 as per Table 8-1, baseline is defined as the last available assessment prior to C1D1.

The investigator will report any vital signs considered clinically significant in the eCRF. For details on AE collection and reporting, refer to AE Section 10.1.1.

As per section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every Y weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

If participants cannot visit the site to have serum pregnancy tests, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment.

A communication process should be established with the participant so that the Site is informed and can verify the pregnancy test results (e.g. following Country specific measures).

If participants cannot visit the site for protocol specified safety lab assessments, an alternative lab (local) collection site may be used.

Table 8-3 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. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement and body temperature.
Height and weight	Height will be measured at screening. Body weight (in indoor clothing, but without shoes) will be measured and BSA will be calculated as specified in Table 8-1.

Performance status:

ECOG Performance status scale will be used as described in Table 8-4 and collected as specified in Table 8-1.

Table 8-4 ECOG performance status

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

8.4.1 Laboratory evaluations

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

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

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.

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

There are no specific notable range criteria for this study; however, the local laboratory will flag laboratory values falling outside of the normal range, on the local report (as applicable) (which the investigator should sign off) as per local practice, and the investigator will report any values considered clinically significant in the eCRF.

Table 8-5 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, MCH, MCHC, MCV, Platelets, Red blood cells, White blood cells, RBC Morphology, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands), Blasts, Other (absolute value preferred, %s are acceptable)
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH),Calcium, Magnesium, Phosphorus, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, Total Protein, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (fasting), Troponin T
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)
Cytokines***	IFN-γ, IL-6, IL-1, TNF-α
Urinalysis dipstick and sediment*	Dipstick examination includes specific gravity, pH, glucose, protein, blood, bilirubin, ketones and WBC as clinically indicated
Pregnancy Test*	Serum / Urine pregnancy test (refer to 'Pregnancy and assessments of fertility' section)
[redacted]	

*Virology, urinalysis and pregnancy test will only be reported in the source documentation.

**Preferred method is erythrocyte folate but in case is not available then serum should be performed. However, every effort should be made to perform both test.

[redacted]

8.4.2 Electrocardiogram (ECG)

Three sequential (triplicate) 12 lead ECGs are to be collected with ECG machines available at the site at Screening and at End of Treatment. Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated (Table 8-6). Unscheduled ECGs with clinically significant findings should be collected in triplicate. Interpretation of the tracing must be made by a qualified physician and documented in the source documents at site. Each ECG tracing should be labeled with the study number, subject initials (where regulations permit), date, and kept in the source documents at the study site. Local cardiologist ECG assessment may also be performed at any time during the study at the discretion of the investigator. Clinically significant abnormalities present at screening should be reported on the appropriate CRF. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

Electrocardiograms (ECGs) must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The individual ECGs should be recorded approximately 3 minutes apart. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

For any ECGs performed in a subject for safety concerns, two additional ECGs must be performed to confirm the safety finding.

Clinically significant abnormalities (including clinically significant ECG findings) must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate. Follow-up in case of QT prolongation should be performed as per Section 6.5.1.2.

Table 8-6 Local ECG collection plan

Visit	Day	Time	ECG Type
Screening	-28 to -1	Anytime	12 Lead
End of Treatment	-	Anytime	12 Lead
Unscheduled or Unplanned sample	-	Anytime	12 Lead

8.4.3 Pregnancy and assessments of fertility

Female patients

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

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

During the study, a urine/serum pregnancy test should be done locally at Day 1 of each cycle (except if for Cycle 1 a pregnancy test was performed within 72 hours of the first dose) and at EOT visit. Additionally, during the post treatment safety follow up, women of child bearing potential will be tested monthly with urine or serum pregnancy tests up to Day 90 after the last dose of azacitidine or decitabine or INQOVI (oral decitabine). They will also be tested monthly with urine or serum pregnancy tests up to Day 150 after the last dose of MBG453 (sabatolimab), and a serum pregnancy test should be performed on Day 150 after the last dose of MBG453 (sabatolimab). If the participant is not coming to the clinic during the safety follow-up period, the test can be performed at home or at a local doctor's office, and the results will be communicated to the site staff.

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.

Women of childbearing potential should employ the use of highly effective contraception during study treatment, for 3 months after the last dose of azacitidine or decitabine or INQOVI (oral decitabine) (or as per their respective local labels, whichever is longer) and 150 days after the last dose of MBG453 (sabatolimab). Highly effective contraception methods are defined in Section 5.2.

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.

Male Patients

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 or decitabine or INQOVI (oral decitabine) and for 3 months after stopping these drugs. In addition, male participants should not donate sperm for the time period specified above.

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

8.4.4 Additional safety monitoring and considerations

Due to the known risk of TLS with azacitidine treatment, during this study, subjects should be closely monitored (including relevant laboratory tests) for signs and symptoms of TLS. High risk patients may need additional measures like i.v. hydration and hospitalization; events should be managed per local guidelines. Refer to Section 6.5.1 for guidance on minimizing the risk of TLS and procedures to be followed before initiation of a treatment cycle and during the treatment cycle.

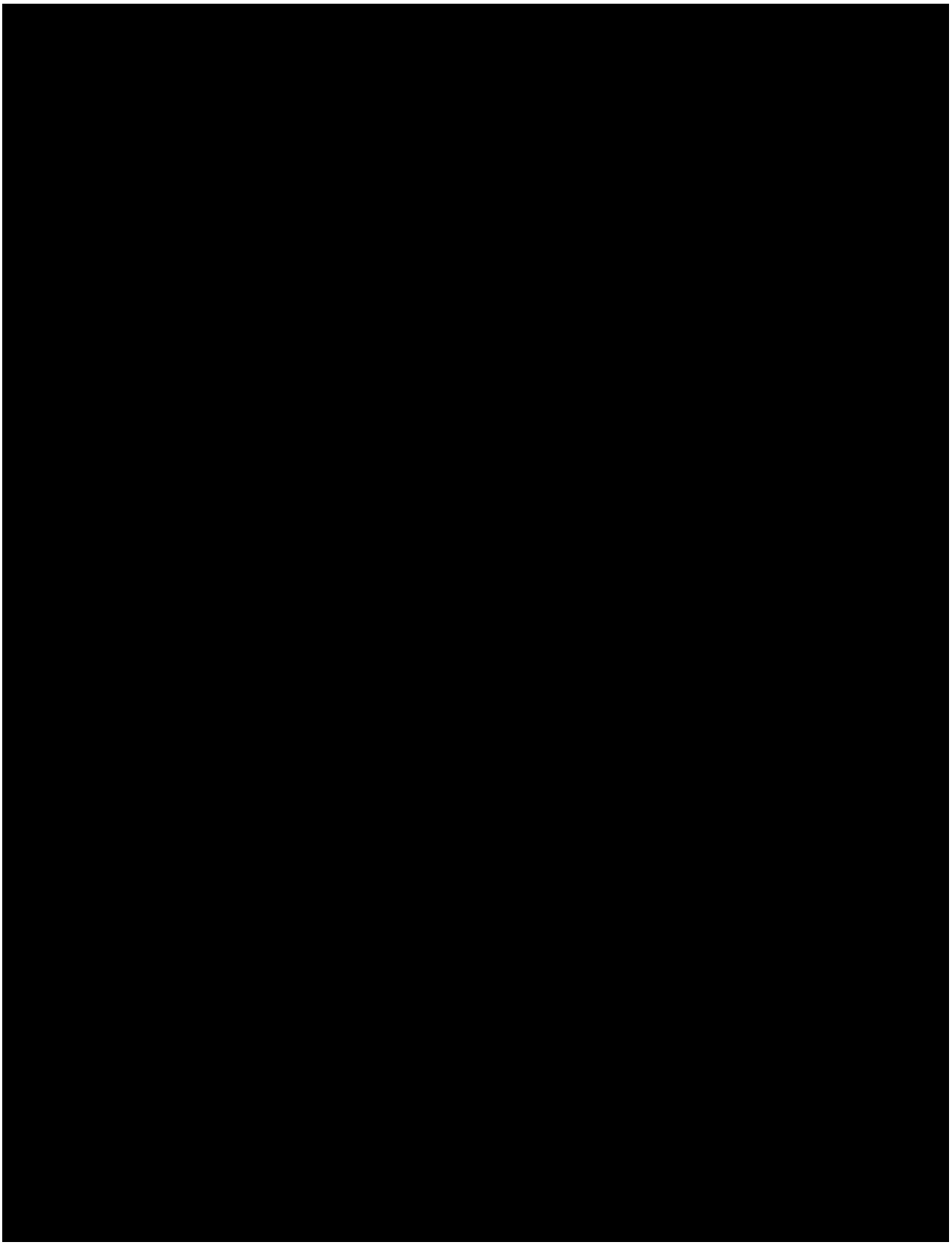
8.4.5 Graft versus Host Disease

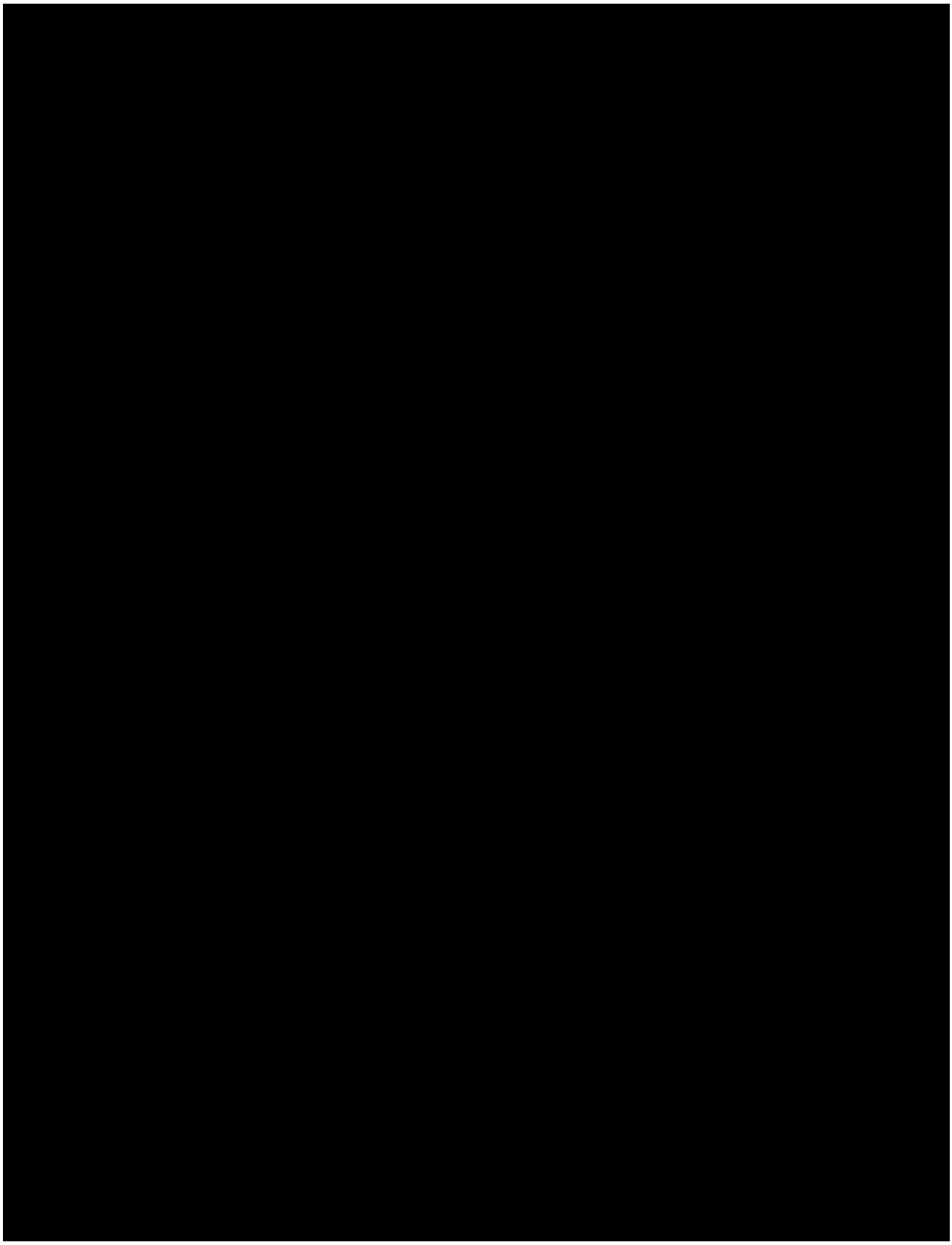
For transplanted patients during post-treatment follow up, [redacted]

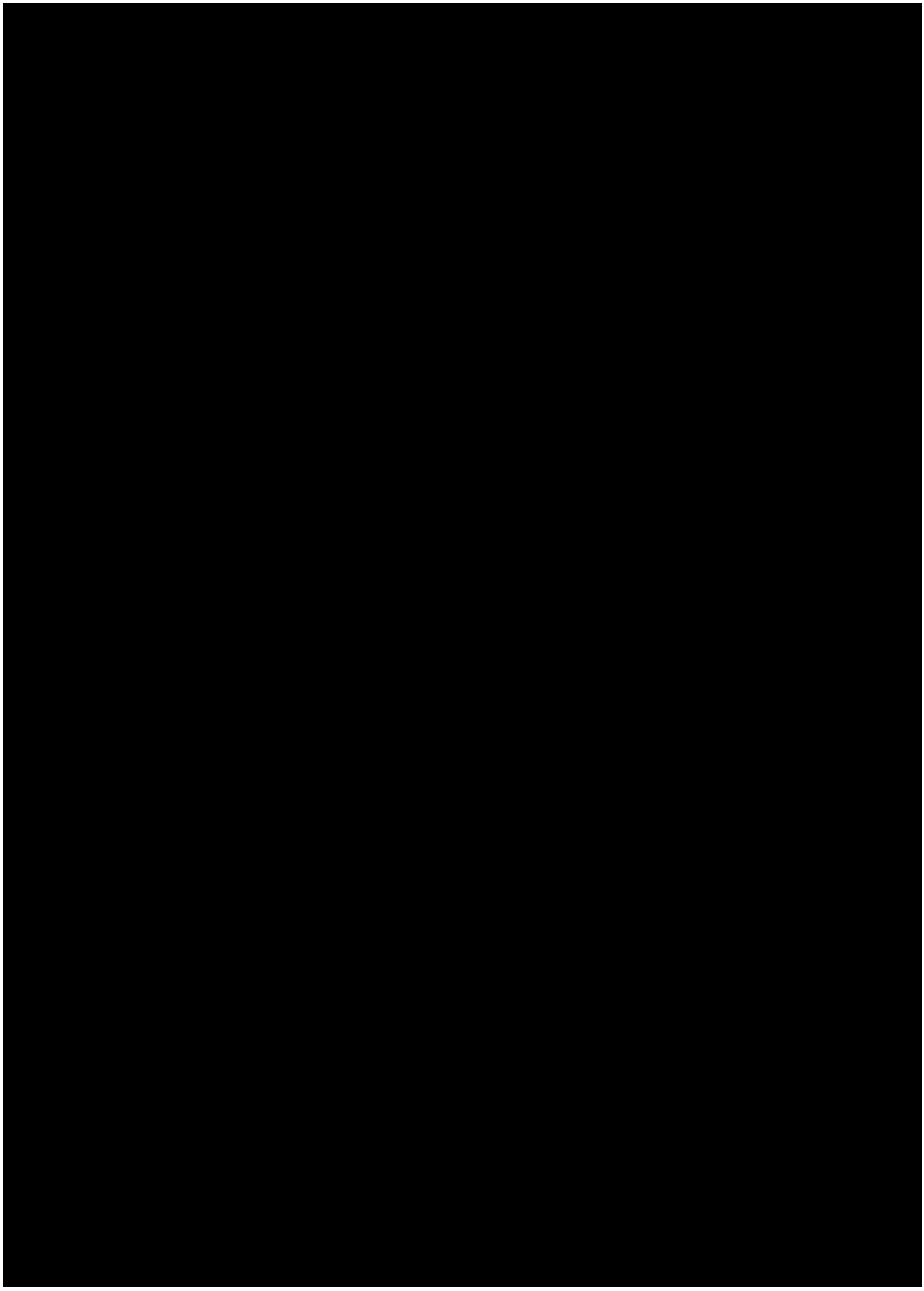
8.4.6 Appropriateness of Safety Measurements

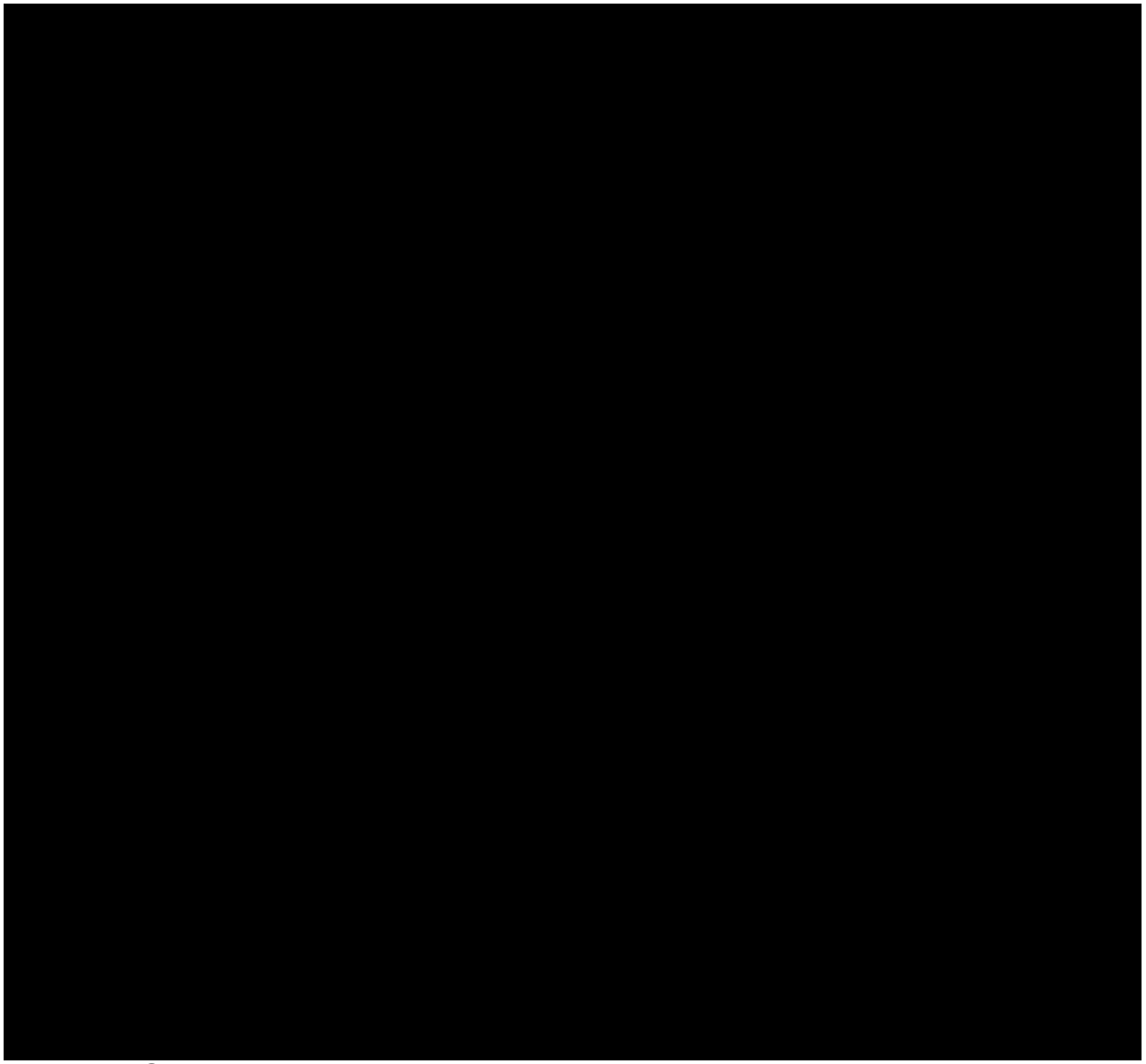
The safety assessments selected are standard for this indication/participant population.

[redacted]









9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Discontinuation of study treatment

Study treatment is consider discontinued if stopped earlier than the protocol planned duration. Either the participant or the investigator can initiate study treatment discontinuation.

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 (see 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 judgement ofthe
- investigator, taking into consideration the participant's overall status, prevents the participant from continuing participation in the study
- Protocol-defined reasons for discontinuation (see Section 6.1.4)
- Progression of disease (including transformation to acute leukemia per WHO 2016 classification, as defined as ≥20% blasts in bone marrow and/or peripheral blood), unless specific criteria to continue study treatment, in case there is no acute leukemia reported, as per Section 6.1.4.1, are met
- Termination of the study by Novartis
- Participants who are scheduled for hematopoietic stem-cell transplant (HSCT) or chemotherapy at any time during the course of the study
- Transition to commercial supplies

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

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see 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 (Section 9.1.3). 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.

For participants who discontinue treatment for reasons other than pregnancy, death, lost to follow-up, or withdrawal of consent, efficacy assessments must continue to be performed every 2 months as per hematology assessment and at least every 6 months as per bone marrow assessment or as clinically indicated until the end of the study, death, lost to follow-up, or withdrawal of consent.

In some circumstances participants may be allowed to continue to receive study treatment beyond disease progression as per criteria described at Section 6.1.4.1. These participants will continue assessments as outlined in the assessments section (Section 8), and will complete the EOT visit only after permanent discontinuation of study treatment.

9.1.2 Withdrawal of informed consent

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

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

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

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 withdrawal. A final evaluation at the time of the participant's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a participant's samples until the time of withdrawal) according to applicable law.

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

9.1.3 Lost to follow-up

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

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible (provide instruction for contacting the participant, when the participant should stop taking drug, when the participant should come for a final visit) and 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.

9.1.5 Extension phase

Patients completing core phase of 12 months and requiring continuation of study treatment (by investigator decision) beyond 1 year will enter the extension phase. For patients that will receive treatment in the extension phase, they are allowed to continue treatment with MBG453 and

azacitidine/decitibine/INQOVI (oral decitibine), azacitidine/decitibine/INQOVI (oral decitibine) alone, or MBG453 alone.

Additionally, for participants who discontinue any study treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent, will enter the extension phase.

Efficacy assessments (hematology and bone marrow aspirate/biopsy) should follow Table 8-1. Response assessments must continue to be performed every 3 cycles as per hematology assessment and at least every 6 cycles as per bone marrow assessment or as clinically indicated until documented disease progression/relapse (per IWG criteria Table 8-2), death, lost to follow-up, or withdrawal of consent.

Drug will be supplied as per section 6.1.4 Also patients who will receive HSCT will be included in the extension phase. Patients will be followed up for efficacy and safety as per Table 8-1 up to 24 months post last patient first treatment. Once they complete the extension phase or end treatment due to progression or any reason excluding HSCT, death, lost to follow up, or withdrawal of consent, patients will enter the post-treatment safety follow up. Participants on the extension period can be contacted by telephone every 6 cycles (24 weeks) to follow-up on their survival status.

9.1.6 Post treatment safety follow up period

Post treatment safety follow up period is for 150 days for safety and until end of study for survival follow up.

All patients on the study should enter the post treatment safety follow up period. Patients can enter the post treatment safety follow up period any time during the study based on discontinuation or completion of prior core phase or extension phase. Reasons for entering the post treatment safety follow up period can be completing the extension phase or ending treatment due to progression. Any new antineoplastic therapies and transfusions that have been started since the previous contact will be collected. HSCT information will also be collected during these phone calls and [redacted] will be collected as part of the safety follow up. Participants on the post treatment safety follow up period can be contacted by telephone every 6 cycles (24 weeks) to follow-up on their survival status.

9.2 Study completion and post-study treatment

Study completion (Core) will occur when the last patient completes the 12 month core phase and safety follow-up or discontinues early.

The end of the study (Last Patient Last Visit) is defined as once all patients discontinued study treatment and were transitioned to treatment outside the study and have completed the study which is targeted at the latest 29 months after the last patient was enrolled. The Last Patient Last Visit will include all the required safety follow-up visits.

At the end of the study, every effort will be made, in alignment with local regulations, to continue provision of MBG453 (sabatolimab) outside this study through an alternative setting to participants who are receiving treatment with MBG453 (sabatolimab) and in the opinion of the investigator are still deriving clinical benefit. Options for continued treatment with MBG453

(sabatolimab) may include access to commercially available drug, or managed access program, or a roll-over study

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

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

- Dose not changed

- Dose Reduced/increased
- Drug interrupted/withdrawn

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

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

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.

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

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

Adverse event monitoring should be continued for at least:

- 30 days following the last dose of azacitidine or decitabine or INQOVI (oral decitabine), or 150 days following the last dose of MBG453 (sabatolimab), whichever is later (After the safety follow-up on site visit on Day 30, participants will be followed via telephone call for the Day 90 and Day 150 (or onsite visit if patient happens to be visiting the site).

OR

- Until the start of a new post treatment antineoplastic medication if sooner than the 150 days mentioned above. If a patient 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 MBG453 (sabatolimab).

Adverse events separate from the progression of malignancy (i.e. deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug. Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

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

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

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

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 judgement 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 medically significant if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

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

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent to 30 days after the date of the last actual administration of HMA

or 150 days after the last dose of MBG453 (sabatolimab), whichever is later and it must be reported to Novartis safety within 24 hours of learning of its occurrence. Any SAEs experienced after the 150 day safety follow-up period should only be reported to Novartis safety database if the investigator suspects a causal relationship to study treatment.

Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

The following SAE reporting timeframes apply:

1. Screen Failures (e.g. a participant who is screened but is not treated or enrolled) SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis
2. Treated participants: SAEs collected between the time the participant signs ICF to 30 days after the date of the last actual administration of HMA or 150 days after the last dose of MBG453 (sabatolimab), whichever is later or stopped study treatment

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. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Disease progression (including fatal outcomes) has to be documented as an efficacy assessment and should not be reported as a serious adverse event, except if the investigator considers that the disease progression is related to study treatment.

If the SAE is not previously documented in the Investigator's Brochure or US Package Insert (new occurrence) and is thought to be related to the study treatment, a Novartis 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.

10.1.4 Pregnancy reporting

If a female subject becomes pregnant, the study treatment should be stopped, and subject must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her pregnancy. To ensure participant safety, each pregnancy occurring in a female study participant 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 12 months after the estimated date of delivery to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same

form and should include an assessment of the possible relationship of the pregnancy outcome and the study treatment. Any SAE experienced during pregnancy must be reported.

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

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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 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

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	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 (Section 10.1.1 and Section 10.1.2).

10.2 Additional Safety Monitoring

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure (IB). Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and must be discussed with the patient during the study as needed.

10.2.1 Steering Committee

The Steering Committee (SC) will be established comprising of investigators participating in the trial and an MDS patient not on the trial.

The Study Steering Committee will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The Study Steering Committee will review protocol amendments as appropriate. Together with the clinical trial team, the Study Steering Committee will also develop recommendations for

publications of study results including authorship rules. The details of the role of the steering committee will be defined in the steering committee charter.

Other members may be added after consultation with SSC members.

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 electronic data capture (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.

11.2 Database management and quality control

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

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

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

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator’s meeting, a Novartis representative or designated CRO will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of

the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

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

Data from all participating centers will be combined. Data from all centers participating in this study will be aggregated for analyses. A contract Research organization will conduct all analyses and will report data from all centers.

The primary analysis of the primary endpoint will be performed after all patients have completed 12 months follow-up from the first dose of study medication or discontinued earlier. A final Clinical Study Report (CSR) will be produced once all patients complete the study.

All AEs, SAEs and other safety parameters will be summarized. No inferential tests for safety analyses will be performed. All primary, secondary [redacted] variables will be summarized descriptively. Categorical data will be presented in frequencies and percentages. For continuous data descriptive statistics (mean, standard deviation, median 25th and 75th percentiles, min and max) will be provided. As appropriate, 95% confidence intervals will also be reported. Kaplan Meier's estimates will be reported for the time to event variables.

Detail analysis methods will be available in the Statistical Analysis Plan (SAP).

12.1 Analysis sets

The analysis sets to be used are defined as below. The FAS will be used as the primary efficacy analysis set. The Safety Set will be used for all the safety analysis.

The screened patients comprises all patients who have signed informed consent/assent and screened in the study. The enrolled comprises all patients who are enrolled in the study. Enrollment is defined as the point at which the patient meets all inclusion/exclusion criteria.

12.1.1 Full Analysis Set (FAS)

The FAS comprises all enrolled patients who receive any component of study medication.

12.1.2 Safety Set (SS)

The Safety Set includes all patients who received at least one dose of study medication..

[redacted]

12.1.5 Efficacy/evaluable set

Not applicable

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be 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 (study treatment, concomitant therapies, compliance)

The duration of exposure will be summarized for study treatment and for each study drug (MBG453 (sabatolimab) and HMA (azacitidine and decitabine and INQOVI (oral decitabine))). 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 for each study drug component by descriptive statistics.

The number of participants with dose adjustments (reductions for HMA only, interruption, or permanent discontinuation) and the reasons will be summarized by study treatment and by study drug.

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

12.4 Analysis of the primary endpoint

12.4.1 Definition of primary endpoint

Primary objective is to assess the safety profile of MBG453 (sabatolimab) 800 mg (every 4 weeks) given in combination with HMAs (IV/SC/ Oral) by 12 months. For all primary safety analyses, the Safety Set will be used, unless stated otherwise. Additionally, safety profile will be assessed beyond the primary time point until the end of the study.

The variables for the primary analysis are incidence and severity of AEs and SAEs, and changes in laboratory values and vital signs.

12.4.2 Statistical model, hypothesis, and method of analysis

No formal hypothesis testing is planned for this study. Analyses of the primary endpoints are described in Section 12.5.2.

12.4.3 Handling of missing values/censoring/discontinuations

Missing data for measures of safety will not be imputed.

12.4.4 Supportive analyses

Subgroup analyses will be performed on the -primary and secondary endpoints of CR and PFS.

The following subgroup analyses may be performed considering patient's baseline status:

- IPSS-R (Intermediate, High & V. High)
- HMA (Oral, IV, SC)

Data will be only summarized within each subgroup.

Additionally, as the study will be ongoing during COVID 19 pandemic, in order to address the impact of COVID-19 (if any) the following will be explored:

- Discontinuation
- Protocol deviation
- Disease status
- Dose interruption/missing data
- AEs and labs

As appropriate, a sensitivity analysis may be performed on the primary safety evaluating the impact of COVID-19 on the study.

12.5 Analysis of secondary endpoints

12.5.1 Secondary objectives

For all secondary efficacy analyses, the Full Analysis Set (FAS) will be used for all patients by 12 months, unless stated otherwise.

12.5.1.1 Complete remission rate

Complete remission rate will be assessed according to International Working Group (IWG) for MDS (2006) with MBG453 (sabatolimab) in combination with HMAs (IV/SC/Oral) in Participants with intermediate, high, or very high risk MDS by 12 months.

Proportion of patients achieving CR by 12 months will be presented together with an exact 95% confidence interval.

Patients who discontinue early before achieving response will be considered as non-responders. Similarly patients with transplant or patients with progression before achieving response will be considered as non-responders. As appropriate, additional sensitivity analyses will be performed excluding discontinued patients, transplant patients and patients with progression before documentation of CR.

12.5.1.2 Progression Free Survival

Progression Free Survival (PFS) rate by 12 months is defined as time from the enrollment date to disease progression (including transformation to leukemia per WHO 2016 classification), relapse from CR according to IWG-MDS or death due to any cause, whichever occurs first, as per investigator assessment during core phase by 12 months post last patient first treatment.

For patients without progression, the time is censored at the latest date the patient was known to be alive and without progression (on or before the cut-off date).

PFS will be analyzed using the Kaplan-Meier Product-Limit method. Patients who do not progress will be censored at the last adequate assessment. Estimates of the 25th, median and 75th percentile of the PFS and their 95% confidence intervals will be provided, if applicable.

12.5.1.3 Overall Survival

Overall Survival (OS) rate by 24 months is defined as the proportion of patients alive time from theenrollment date to death due to any cause during 12 months.

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

OS will be analyzed using the Kaplan-Meier Product-Limit method. Patients who do not die will be censored at the last adequate assessment. Estimates of the 25th, median and 75th percentile of the OS and their 95% confidence intervals will be provided, if applicable.

12.5.1.4 Leukemia-free survival

Leukemia-free survival (LFS) is the time from the enrollment date to $\geq$ 20% blasts in bone marrow/peripheral blood (per WHO 2016 classification) or death due to any cause.

For a patient without event, the time is censored at the latest date the patient was known to be alive and without leukemia (on or before the cut-off date).

LFS will be analyzed using the Kaplan-Meier Product-Limit method. Patients who are not known to be alive without leukemia will be censored at the last adequate assessment. Estimates

of the 25th, median and 75th percentile of the PFS and their 95% confidence intervals will be provided, if applicable.

12.5.1.5 Other Response Rates

CR/mCR/PR according to IWG-MDS will be as per investigator assessment. Number and percentage patients with all other responses rates will be summarized.

12.5.1.6 Duration to Complete Remission

Duration of Complete Remission (DOR) is the time from the date of the first documented CR to the date of first documented relapse from CR or death due to any cause, whichever occurs first.

The start date is the date of first documented CR and the end date is defined as the date of the first documented relapse from CR or death due to any cause. Participants continuing without event will be censored at the date of their last adequate response assessment.

DOR will be listed and summarized. Median duration and 95% Confidence interval will be reported.

12.5.1.7 Time to Complete Remission

Time to Complete Remission is defined as the time from the date of enrollment to the first documented CR.

Time to complete remission will be analyzed using the Kaplan-Meier Product-Limit method. Patients who are known to be without CR will be censored at the last adequate assessment. Estimates of the 25th, median and 75th percentile of the PFS and their 95% confidence intervals will be provided, if applicable.

12.5.1.8 Improvement in RBC/platelets transfusion independence

Number and percent of patients who are RBC/platelets transfusion independent after the date of the first dose of study medication as per IWG-MDS.

RBC/Platelets transfusion independence rate is defined as the proportion of participants having received <0 units RBC/Platelets transfusions during at least 8 consecutive weeks after enrollment (Table 8-2). The number and percentage of patients will be shown for the overall FAS and then also in only those with transfusion dependence at baseline. Percentages will be provided with exact 95% Clopper-Pearson confidence intervals.

For participants with at least one period of transfusion independence post-baseline, the total duration of all transfusion independence periods (which all individually must be at least 8 weeks) will be also summarized.

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

12.5.2 Safety objectives

12.5.2.1 Analysis set and grouping for the analyses

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

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

- pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
- on-treatment period: from day of first dose of study medication to last dose of study medication and up to 30 days after last dose.
- Post-treatment period: starting at day 31 after last administration of study treatment (MBG453 or HMA)
- Note : for patients who discontinue MBG453 investigational study treatment to receive transplant, they will not be included in the safety set (post discontinuation) and only be followed up for [redacted] transplant related mortality.

12.5.2.2 Adverse events (AEs)

All information obtained on adverse events will be displayed by treatment and participant.

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period. The number (and percentage) of participants with treatment emergent AEs will be summarized by primary system organ class, preferred term and maximum severity (based on CTCAE grades). Separate summaries will be provided for study medication related adverse events, deaths, serious adverse events, adverse events leading to treatment discontinuation, and adverse events leading to dose adjustment. The number (and percentage) of participants with 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, adverse events leading to treatment discontinuation, and adverse events leading to dose adjustment.

The incidence of adverse events will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment.

Serious adverse events and non-serious adverse events will be tabulated.

Selected summaries of adverse events will be produced for the overall safety period. All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths, and serious adverse events (including those from the pre- and post-treatment periods) will be listed and those collected during the pre-treatment, post-treatment and overall safety period will be flagged.

12.5.2.3 Laboratory abnormalities

Grading of laboratory values will be assigned programmatically as per NCI 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. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE v5, results will be categorized as low/normal/high (or other project-specific ranges, if more suitable) based on laboratory normal ranges.

The following summaries will be generated separately for hematology and biochemistry tests:
For laboratory tests where grades are defined by CTCAE v5

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.
- Shift tables to compare baseline CTCAE grades to the worst on-treatment grade

For laboratory tests where grades are not defined by CTCAE v5

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

Listing of all laboratory data with values flagged to show the corresponding CTCAE v5 grades if applicable and the classifications relative to the laboratory normal ranges will be presented.

12.5.2.4 Other safety data ECG

A 12-lead ECG including PR, QRS, QT, QTcF, QTcB and RR intervals will be obtained for each patient during the study.

As appropriate, the number and percent of patients with notable ECG value will be tabulated by category. In addition, a listing of patients with at least one notable ECG value will be produced.

Vital signs

Data on vital signs will be tabulated and summarized descriptively as follows:

- Change from baseline to the worst on-treatment result
- Number and frequency of patients who shift from non-notable at baseline to notable post-baseline (details about the definition of notable abnormal results will be given in the SAP)

All information collected will be listed and notable values will be flagged.

[redacted]

[redacted]

- [redacted],
- [redacted]

12.6 Interim analyses

As appropriate, interim analyses may be performed for publication or any regulatory purpose.

The study primary analysis will be by 12 months post last patient first treatment and a CSR will be written. Additional Final Analyses maybe performed when all patients complete the extension phase and safety follow up. In this case, the final CSR will be written.

12.7 Sample size calculation

This is an open label, non-randomized, single-arm combination study to assess safety and efficacy of MBG453 (sabatolimab) given with HMAs of investigator's choice (IV/ SC/ Oral). The primary objective of the study is to assess safety profile of this combination drug by 12 months.

Given the above expected incidence rates of AEs with the combination (Table 1-3), a sample size of 81 evaluable patients was estimated based on a two sided 95% confidence interval for an incidence rate of an AE using the large sample normal approximation that will extend 0.10 from the observed incidence rate of an AE (precision or margin of error of 10%) for an expected incidence rate of 30%.

Novartis has decided to permanently halt recruitment based on a reevaluation of the development strategy for sabatolimab. Patients who are currently on study treatment or in follow-up will be continue per the protocol. At the time of this amendment, 39 patients have been enrolled into the study.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC/REB

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 field 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 Informed consent procedures

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

Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents. The date when a patient's Informed Consent was actually obtained will be captured in their eCRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential must be informed that taking the study medication 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 requirement for the duration of the study. If there is any question that the patient will not reliably comply, they must not be entered in the study.

13.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 9.1.4.

13.5 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov. 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, FDA 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.

13.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of patients. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the Sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and patient files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study electronic case report form (eCRF) is the primary data collection instrument for the study. The investigator must ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF, that are derived from source documents, must be consistent with the source documents or the discrepancies must be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. For electronic CRFs an audit trail will be maintained by the system.

The investigator/institution must maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution must take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) must be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

13.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

13.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

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

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

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

13.9 Financial disclosures

Financial disclosures must be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

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. All significant protocol deviations will be recorded and reported in the CSR.

14.1 Amendments to the protocol

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.

15 References

Aaronson NK, Ahmedzai S, Bergman B, et al (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst; 85(5): 365-76.

[redacted]

Arber DA, Orazi A, Hasserjian R, et al (2016) The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood; 127(20): 2391-405.

Asayama T, Tamura H, Ishibashi M, et al (2017) Functional expression of Tim-3 on blasts and clinical impact of its ligand galectin-9 in myelodysplastic syndromes. Oncotarget; 8(51): 88904-17.

[redacted]

Bell JA, Galaznik A, Blazer M, et al (2018) Transfusion-free interval is associated with improved survival in patients with higher-risk myelodysplastic syndromes engaged in routine care. Leuk Lymphoma; 60(1): 1-11

Bergman B, Aaronson NK, Ahmedzai S, et al (1994) The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. Eur J Cancer; 30A(5): 635-42.

Borate U, Esteve J, Porkka K, et al (2019) Phase Ib Study of the Anti-TIM-3 Antibody MBG453 in Combination with Decitabine in Patients with High-Risk Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML). ASH Annual Meeting 2019

Borate U, Esteve J, Porkka K, et al (2019) Anti-TIM-3 Antibody MBG453 in combination with hypomethylating agents (HMAS) in patients (PTS) with high-risk myelodyplastic syndrome (HR-MDS) and acute myeloid leukemia (AML). EHA Annual Meeting 2020.

Brahmer JR, Lacchetti C, Schneider BJ, et al (2018) Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol; 36(17): 1714-1768.

Bretz F, Maurer W, Brannath W, et al (2009) A graphical approach to sequentially rejective multiple test procedures. Stat Med; 28(4): 586-604.

Bretz F, Posch M, Glimm E, et al (2011) Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. Biom J; 53(6): 894-913.

Cairo MS, Bishop M (2004) Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol; 127(1): 3-11.

Chen J, Kao YR, Sun D, et al (2019) Myelodysplastic syndrome progression to acute myeloid leukemia at the stem cell level. Nat Med; 25(1): 103-10.

Chen X, Liu S, Wang L, et al (2008) Clinical significance of B7-H1 (PD-L1) expression in human acute leukemia. Cancer Biol Ther; 7(5): 622-7.

Cheson BD, Bennett JM, Kantarjian H, et al (2000) Report of an international working group to standardize response criteria for myelodysplastic syndromes. Blood; 96(12): 3671-4.

Cheson BD, Greenberg PL, Bennett JM, et al (2006) Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood; 108(2): 419-25.

Chou FC, Kuo CC, Chen HY, et al (2016) DNA demethylation of the TIM-3 promoter is critical for its stable expression on T cells. Genes Immun; 17(3): 179-86.

Clopper CJ and Pearson ES (1934) The use of confidence or fiducial limites illustrated in the case of the binomial. Biometrika; 26(4): 404-413

Cogle C, Scott B, Boyd T, et al (2015) Oral Azacitidine (CC-486) for the Treatment of Myelodysplastic Syndromes and Acute Myeloid Leukemia. Oncologist; 20(12): 1404-12

Coiffier B, Altman A, Pui CH, et al (2008) Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol; 26(16): 2767-78.

Curigliano G, Gelderblom H, Mach N, (2019) Abstract CT183: Phase (Ph) I/II study of MBG453 ± spartalizumab (PDR001) in patients (pts) with advanced malignancies. AACR Annual Meeting 2019

Daver N, Garcia-Manero G, Basu S, et al (2018) Efficacy, Safety, and Biomarkers of Response to Azacitidine and Nivolumab in Relapsed/Refractory Acute Myeloid Leukemia: A Nonrandomized, Open-Label, Phase II Study. Cancer Discov.

Derissen EJ, Beijnen JH, Schellens JH (2013) Concise drug review: azacitidine and decitabine. Oncologist; 18(5): 619-24.

Dominietto A, Lamparelli T, Raiola A, et al (2002) Transplant-related mortality and long-term graft function are significantly influenced by cell dose in patients undergoing allogeneic marrow transplantation. Blood; 100(12): 3930-3934.

Fayers PM (2001) Interpreting quality of life data: population-based reference data for the EORTC QLQ-C30. Eur J Cancer; 37(11): 1331-4.

Fenaux P, Haase D, Sanz GF, et al (2014) Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol; 25(suppl_3): iii57-69.

Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al (2009) Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol; 10(3): 223-32.

Freeman SD, Hills RK, Virgo P, et al (2018) Measurable Residual Disease at Induction Redefines Partial Response in Acute Myeloid Leukemia and Stratifies Outcomes in Patients at Standard Risk Without NPM1 Mutations. J Clin Oncol; 36(15): 1486-1497.

Freeman SD, Virgo P, Couzens S, et al (2013) Prognostic relevance of treatment response measured by flow cytometric residual disease detection in older patients with acute myeloid leukemia. J Clin Oncol; 31(32): 4123-31.

Gail J Roboz, Pau Montesinos, Dominik Selleslag et al (2016); Design of the randomized, Phase III, QUAZAR AML Maintenance trial of CC-486 (oral azacitidine) maintenance therapy in acute myeloid leukemia future Oncology

Garcia-Manero G, Sasaki K, Montalban-Bravo G, et al (2018) A Phase II Study of Nivolumab or Ipilimumab with or without Azacitidine for Patients with Myelodysplastic Syndrome (MDS) p. ASH Annual Meeting 2018.

Garcia-Manero, G (2019). The Clinical Trials of the Combinations of HMAs with ICPIs in Patients with MDS. MDS int'l symposium.

Garcia-Manero G, Jonasova A, Luger S, et al (2019) Genomic Profiling in Patients with Higher-Risk Myelodysplastic Syndrome (HR-MDS) Following HMA Failure: Baseline Results from the Inspire Study (04-30). Blood; 134(1): 3015

Garcia-Manero G, Shan J, Faderl S, et al (2008) A prognostic score for patients with lower risk myelodysplastic syndrome. Leukemia; 22(3): 538-43.

Garcia-Manero G, McCloskey J, Griffiths E, et al (2019) Pharmacokinetic Exposure Equivalence and Preliminary Efficacy and Safety from a Randomized Cross over Phase 3 study (ASCERTAIN study) of an Oral Hypomethylating Agent ASTX727 (cedazuridine/decitabine) compared to IV Decitabine. ASH Annual Meeting 2019.

Garcia-Manero G, Santini V, Almeida A, et al (2020) A Phase III Placebo-controlled Trial of CC-486 in Patients with Red Blood Cell Transfusion-dependent (RBC-TD) Anemia and Thrombocytopenia Due to IPSS Lower-risk Myelodysplastic Syndromes (LR-MDS). EHA Annual Meeting 2020.

Gonçalves Silva I, Yasinska IM, Sakhnevych SS, et al (2017) The Tim-3-galectin-9 Secretory Pathway is Involved in the Immune Escape of Human Acute Myeloid Leukemia Cells. EBioMedicine; p. 44-57.

Greenberg PL, Tuechler H, Schanz J, et al (2012) Revised international prognostic scoring system for myelodysplastic syndromes. Blood; 120(12): 2454-65.

Heaney ML, Golde DW (1999) Myelodysplasia. N Engl J Med; 340(21): 1649-60.

[redacted]

Ivey A, Hills RK, Simpson MA, et al (2016) Assessment of Minimal Residual Disease in Standard-Risk AML. N Engl J Med; 374: 422-33.

Jan M, Chao MP, Cha AC, et al (2011) Prospective separation of normal and leukemic stem cells based on differential expression of TIM3, a human acute myeloid leukemia stem cell marker. Proc Natl Acad Sci USA; 108(12): 5009-14.

Jing W, Gershan JA, Weber J, et al (2015) Combined immune checkpoint protein blockade and low dose whole body irradiation as immunotherapy for myeloma. J Immunother Cancer; 3(1): 2.

Jongen-Lavrencic M, Grob T, Hanekamp D, et al (2018) Molecular Minimal Residual Disease in Acute Myeloid Leukemia. N Engl J Med; 378: 1189-1199.

Eric Laille, Michael R. Savona, Bart L. Scott et al (2014) Pharmacokinetics of Different Formulations of Oral Azacitidine (CC‐486) and the Effect of Food and Modified Gastric pH on Pharmacokinetics in Participants With Hematologic Malignancies; journal of clinical pharmacology

Kantarjian H, Issa JP, Rosenfeld CS, et al (2006) Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. Cancer; 106(8): 1794-803.

Kuendgen A, Nomdedeu M, Tuechler H, et al (2020) Therapy-related myelodysplastic syndromes deserve specific sub-classification and risk-stratification—an approach to classification of patients with t-MDS. Leukemia, online. (https://doi.org/10.1038/s41375-020-0917-7)

Kikushige Y, Miyamoto T, Yuda J, et al (2015) A TIM-3/Gal-9 Autocrine Stimulatory Loop Drives Self-Renewal of Human Myeloid Leukemia Stem Cells and Leukemic Progression. Cell Stem Cell; 17(3): 341-52.

Kikushige Y, Shima T, Takayanagi S, et al (2010) TIM-3 is a promising target to selectively kill acute myeloid leukemia stem cells. Cell Stem Cell; 7(6): 708-17.

Kim K, DeMets DL (1987) Design and analysis of group sequential tests based on the type I error spending rate function. Biometrika; 74(1): 149-154.

Klepin HD (2016) Myelodysplastic Syndromes and Acute Myeloid Leukemia in the Elderly. Clin Geriatr Med; 32(1): 155-73.

Komrokji R (2015) Treatment of Higher-Risk Myelodysplastic Syndromes After Failure of Hypomethylating Agents. Clinical Lymphoma Myeloma and Leukemia; 15: (S56-S59)

Komrokji RS, DeZern AE, Zell K et al Validation of International Working Group (IWG) Response Criteria in Higher-Risk Myelodysplastic Syndromes (MDS): A Report on Behalf of the MDS Clinical Research Consortium (MDS CRC). Blood; 126(23): 909

Kong Y, Zhang J, Claxton DF, et al (2015) PD-1(hi)TIM-3(+) T cells associate with and predict leukemia relapse in AML patients post allogeneic stem cell transplantation. Blood Cancer J; 31(5): e330

Makishima H, Yoshizato T, Yoshida K, et al (2017) Dynamics of clonal evolution in myelodysplastic syndromes. Nat Genet; 49(2): 204-212.

Mo XD, Qin YZ, Zhang XH, et al (2016) Minimal residual disease monitoring and preemptive immunotherapy in myelodysplastic syndrome after allogeneic hematopoietic stem cell transplantation. Ann Hematol; 95(8): 1233-40.

Nazha A, Sekeres MA, Garcia-Manero G, et al (2016) Outcomes of patients with myelodysplastic syndromes who achieve stable disease after treatment with hypomethylating agents. Leuk Res; 41: 43-7.

Ngiow SF, Teng MW, Smyth MJ (2011) Prospects for TIM3-Targeted Antitumor Immunotherapy. Cancer Res; 71(21): 6567-71.

Papaemmanuil E, Gerstung M, Malcovati L, et al (2013) Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood; 122(22): 3616-27.

Passweg JR, Zhang MJ, Rocha V, et al (2011) Donor characteristics affecting graft failure, graft-versus-host disease, and survival after unrelated donor transplantation with reduced-intensity conditioning for hematologic malignancies. Biol. Blood Marrow Transplant; 17(12): 1869-73.

Platzbecker U (2019) Treatment of MDS. Blood; [Epub ahead of print].

Platzbecker U, Fenaux P, Adès L, et al (2018) Proposals for revised IWG 2018 hematological response criteria in patients with MDS included in clinical trials. Blood; [Epub ahead of print].

Pocock SJ (1977) Group sequential methods in the design and analysis of clinical trials. Biometrika; 64(2): 191-99.

[redacted]

Sakuishi K, Apetoh L, Sullivan JM, et al (2010) Targeting Tim-3 and PD-1 pathways to reverse T cell exhaustion and restore anti-tumor immunity. J Exp Med; 207(10): 2187-94.

Sakuishi K, Jayaraman P, Behar SM, et al (2011) Emerging Tim-3 functions in antimicrobial and tumor immunity. Trends Immunol; 32(8): 345-9.

Saunthararajah Y (2013) Key clinical observations after 5-azacytidine and decitabine treatment of myelodysplastic syndromes suggest practical solutions for better outcomes. Hematology Am Soc Hematol Educ Program; 2013(1): 511-21.

Silverman LR, Demakos EP, Peterson BL, et al (2002) Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B J Clin Oncol; 20(10): 2429-40.

Sohlberg E, Pfefferle A, Andersson S, et al (2015) Imprint of 5-azacytidine on the natural killer cell repertoire during systemic treatment for high-risk myelodysplastic syndrome. Oncotarget; 6(33): 34178-90.Steensma DP (2018) Myelodysplastic syndromes current treatment algorithm 2018. Blood Cancer J; 8(5): 47.

Stein E, Latremouille-Viau, D, et al (2019) Treatment Patterns and Outcomes in Patients with Myelodysplastic Syndromes Treated with Gypomethylating Agents: A SEER-Medicare Analysis. ASH 2019 Poster.

Tao JL, Li LJ, Fu R, et al (2014) Elevated TIM3+ hematopoietic stem cells in untreated myelodysplastic syndrome displayed aberrant differentiation, overproliferation and decreased apoptosis. Leuk Res; 38(6): 714-21.

Terwijn M, van Putten WL, Kelder A, et al (2013) High prognostic impact of flow cytometric minimal residual disease detection in acute myeloid leukemia: data from the HOVON/SAKK AML 42A study. J Clin Oncol; 31(31): 3889-97.

[redacted]

Yang H, Bueso-Ramos C, DiNardo C, et al (2014) Expression of PD-L1, PD-L2, PD-1 and CTLA4 in myelodysplastic syndromes is enhanced by treatment with hypomethylating agents. Leukemia; 28(6): 1280-8.

Yellen S, Cella D, Webster K, et al (1997) Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. J Pain Symtpom Manage; 13(2): 63-74.

Zeidan AM, Davidoff AJ, Long JB, et al (2016) Comparative clinical effectiveness of azacitidine versus decitabine in older patients with myelodysplastic syndromes. Br J Haematol; 175(5): 829-840.

Zeidan AM, Knaus HA, Robinson TM, et al (2018) A Multi-center Phase I Trial of Ipilimumab in Patients with Myelodysplastic Syndromes following Hypomethylating Agent Failure. Clin. Cancer Res; 24(15): 3519-3527.

Zhang L, Gajewski TF, Kline J (2009) PD-1/PD-L1 interactions inhibit antitumor immune responses in a murine acute myeloid leukemia model. Blood; 114(8): 1545-52.

Ørskov AD, Treppendahl MB, Skovbo A, et al (2015) Hypomethylation and up-regulation of PD-1 in T cells by azacytidine in MDS/AML patients: A rationale for combined targeting of PD-1 and DNA methylation. Oncotarget; 6(11): 9612-26.

16 Appendices

MBG453, as a mAB, is not expected to have many interactions, unlike small molecules that are metabolized by the CYP450 enzymes and may induce or inhibit some of these enzymes or other transporters. Therefore, there is no long list of prohibited meds that need to be listed in an appendix. Please refer to section 6.2.2.

16.1 Appendix 1: Clinically notable laboratory values and vital signs

There are no specific notable range criteria for this study; however, the local and central laboratory will flag laboratory values falling outside of the normal range, on the local and central laboratory report (as applicable) (which the investigator should sign off) as per local practice, and the investigator will report any values considered clinically significant in the eCRF. The investigator will also report any vital signs, local ECG values considered clinically significant in the eCRF.

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

Table 16-1 Liver event and laboratory trigger definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	3 x ULN <ALT / AST ≤ 5 x ULN 1.5 x ULN <TBL ≤ 2 x ULN
LIVER EVENTS	ALT or AST >5 × ULN
	ALP >2 × ULN (in the absence of known bone pathology)
	TBL >2 × ULN (in the absence of known Gilbert syndrome)
	ALT or AST >3 × ULN and INR >1.5
	Potential Hy's Law cases (defined as ALT or AST >3 × ULN and TBL >2 × ULN [mainly conjugated fraction] without notable increase in ALP to >2 × ULN)
	Any clinical event of jaundice (or equivalent term)
	ALT or AST >3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
	Any adverse event potentially indicative of a liver toxicity*
*These events cover the following: Hepatic failure, fibrosis and cirrhosis, and other liver damage- related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL: total bilirubin; ULN: upper limit of normal	

Table 16-2 Follow up requirements for liver laboratory triggers with liver symptoms

Criteria	**Actions required**	**Follow-up monitoring**
Potential Hy's Law case[a]	Discontinue the study treatment immediately Hospitalize, if clinically appropriate Establish causality Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
ALT or AST		
>8 × ULN	Discontinue the study treatment immediately Hospitalize if clinically appropriate Establish causality Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
>3 × ULN and INR >1.5	Discontinue the study treatment immediately Hospitalize, if clinically appropriate Establish causality Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
>5 to ≤8 × ULN	Repeat LFT within 48 hours If elevation persists, continue follow-up monitoring If elevation persists for more than 2 weeks, discontinue the study drug Establish causality Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
>3 × ULN accompanied by symptoms[b]	Discontinue the study treatment immediately Hospitalize if clinically appropriate Establish causality Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

>3 to ≤5 × ULN (patient is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks

Criteria	Actions required	Follow-up monitoring
ALP (isolated)		
>2 × ULN (in the absence of known bone pathology)	Repeat LFT within 48 hours If elevation persists, establish causality Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
>2 × ULN (in the absence of known Gilbert syndrome)	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
>1.5 to ≤2 × ULN (patient is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	Discontinue the study treatment immediately Hospitalize the patient Establish causality Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	Consider study treatment interruption or discontinuation	Investigator discretion

	Hospitalization if clinically	

Criteria	Actions required	Follow-up monitoring
[a]Elevated ALT/AST >3 × ULN and TBL >2 × ULN but without notable increase in ALP to >2 ×ULN [b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia [c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.		

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

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** (PCR) ≥ 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, tumorlysis

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 PCR <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: Eligibility based on serologic markers for hepatitis B

Please consider the general guidelines below, investigators may consult specialists to decide participant's eligibility in case of borderline results.

Protocol exclusion criterion:

- Positive serology for hepatitis B surface antigen (HBsAg)
- Positive serology for hepatitis B core antibody (HBcAb), except if both criteria are met:
  1. HBV DNA negative
  2. Hepatitis B monitoring is implemented: HBsAg and HBV DNA should be tested every 6 weeks for the first 6 months and every 12 weeks thereafter, until the end of study.

Table 16-5 Eligibility based on serologic markers for hepatitis B

HBsAg	HBcAb	HBV DNA	Eligible	Comment
-	-	-	Yes	
-	+	-	Yes	Prophylaxis + monitoring
-	+	+	No	Consider treatment
+	+	+	No	Consider treatment

Table 16-6 Decision tree to determine eligibility based on serologic markers for hepatitis B