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Novartis Research and Development

MBG453

Clinical Trial Protocol CMBG453B12301 / NCT04266301

A randomized, double-blind, placebo-controlled phase III multi-center study of azacitidine with or without MBG453 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)

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List of abbreviations

ADA	Anti-drug Antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
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
CFR	Code of Federal Regulation
CI	Confidence interval
CK	Creatinine kinase
CMML	Chronic myelomonocytic leukemia
COA	Clinical Outcome Assessment
COVID-19	Coronavirus disease of 2019
CR	Complete Remission
CRi	Complete Remission with incomplete hematologic recovery
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTLA4	Cytotoxic T-lymphocyte-associated Protein 4
CV	Coefficient of variation
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report/Record Form
EDC	Electronic Data Capture
eGFR	estimated Glomerular Filtration Rate
EHA	European Hematology Association
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer - Quality of Life Questionnaire
EOT	End of treatment
ePRO	Electronic Patient Reported Outcome
EQ-5D-5L	EuroQol Group - standardized measure of health status questionnaire
ESMO	European Society for Medical Oncology
FACIT	Functional Assessment of Chronic Illness Therapy

[redacted]

FAS	Full Analysis Set
FDA	Food and Drug Administration
FUP	Follow Up
G-CSF	Granulocyte Colony Stimulating Factor
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLDH	Glutamate dehydrogenase
h	Hour
HBcAB	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HgB	Hemoglobin
HI	Hematologic improvement
HIV	Human immunodeficiency virus
HMA	Hypomethylating agent
HR	Hazard ratio
HSCT	Hematopoietic Stem-Cell Transplantation
i.v. or IV	Intravenous
IA	Interim Analysis
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IG	Immunogenicity
INR	International normalized ratio
IPSS-R	Revised International Prognostic Scoring System
irAE	Immune related adverse event
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine System
IWG	International Working Group
LDH	Lactate dehydrogenase
LFT	Liver function test
LPLV	Last Patient Last Visit
MAP	Meta-analytic-predictive
MCH	Mean cell hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
mCR	marrow Complete Remission
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndromes
MedDRA	Medical dictionary for regulatory activities
[redacted]	[redacted]
mg	milligram(s)

[redacted]

mL	milliliter(s)
[redacted]	[redacted]
NB	negative binomial
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
[redacted]	[redacted]
NR	Not reached
ORR	Overall Response Rate
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PB	Peripheral blood
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic(s)
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death 1 ligand
PD-L2	Programmed cell death 2 ligand
PFS	Progression Free Survival
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PK	Pharmacokinetic(s)
PoS	Probability of Success
PR	Partial remission
PRO	Patient Reported Outcome
PS	Performance status
PSDS	Post Study Drug Supply
PTA	Post Trial Access
Q2W	Every 2 weeks
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QoL	Quality of life
QTcF	Corrected QT interval by Fridericia
RBC	Red blood cell(s)
RNA	Ribonucleic acid
s.c.	Subcutaneous
SAE	Serious adverse event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SC	Steering Committee
sCR	serum creatinine
SCT	Stem cell transplant
SD	Stable disease
SOC	Standard of Care
sTIM-3	Soluble T-cell immunoglobulin domain and mucin domain-3
SUSAR	Suspected Unexpected Serious Adverse Reactions

[redacted]

TBL	Total bilirubin
TFI	Transfusion-free interval
TFR	Transfusion-free rate
TIM-3	T-cell immunoglobulin domain and mucin domain-3
TLS	Tumor lysis syndrome
TSH	Thyroid-Stimulating Hormone
TTDD	Time to definitive deterioration
ULN	Upper limit of normal
VAS	Visual analogue scale
WBC	White blood cell(s)
WHO	World Health Organization

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biological Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
Combination drug	Any drug that is combined to a specified regimen
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Discontinuation from study	Point/time when the subject permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participants agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Enrollment	Point/time of subject entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol).
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.
Estimands	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable
Intercurrent Events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product”.
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.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest
Patient Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient about the status of a participant's health condition without amendment or interpretation of the patient's report by a clinician or anyone else

[redacted]

Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location
Screen Failure	A subject who is screened but is not treated or randomized
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study treatment	Any drug 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 subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints.
Withdrawal of consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when a subject explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

[redacted]

Amendment 3 (23-Jun-2022)

Amendment rationale

The purpose of this protocol amendment is to adjust the group-sequential statistical plan based on independent information that became available from the final progression free survival (PFS) analysis of CMBG453B12201 which was conducted in a similar patient population and study treatment. Based on these data, a delayed treatment effect is considered for this study which justifies an increase in overall survival (OS) events to retain statistical power for the primary analysis at 85%.

As of the release of this amendment, accrual was completed: 530 patients have been randomized. The DMC, who has been informed about the outcome of CMBG453B12201, had completed the safety & preplanned futility assessment of this study at 74 OS events (data cutoff as of 20Nov2021) and recommended to continue the trial.

- CMBG453B12201 is a phase II randomized study in 127 patients with MBG453 or placebo added to hypomethylating agents in adult subjects with intermediate, high or very high risk myelodysplastic syndrome as per IPSS-R criteria. Final PFS analysis results from CMBG453B12201 indicated an unanticipated possible 5-months delayed treatment effect for PFS in the investigational arm compared to the control arm. Also, for OS a delayed onset of effect is suspected.
- If a delayed treatment effect of this magnitude be found in this study, it would result in a substantial loss of statistical power for the OS analysis (refer to Section 12.8 for statistical analysis and assumptions); therefore, the study design is revised to preserve statistical power at 85%.
- In order to achieve a statistical power of 85%, based on assumption of 5 months delayed treatment effect and followed by an effect of the same magnitude as assumed in the protocol version 00 (i.e. HR=0.6), the number of OS events for the primary analysis is increased from 180 to approximately 282 events.
- The interim analysis on survival will be conducted when 135 OS events have been documented as per protocol v00 planned number of events. This interim analysis is planned to be conducted shortly after protocol amendment 03 finalization.
- The delay of the primary analysis timepoint is not likely to present an additional risk for patients based on MBG453 safety profile. Regular safety reviews will be conducted by the DMC.

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.

- Protocol summary, Section 3, Section 4.4 and Section 12: Revised the number of OS events for the primary analysis and updated Table 12-2
- Section 9.1.1: Removed reporting period for concomitant treatments (to avoid inconsistency with Section 6.2.1)
- Section 10.1.3: Added that SAE reporting timelines may be adjusted as per local requirements

[redacted]

- Section 12.7: With increase from 180 to 282 OS events, the information fraction corresponding to the 135 events planned for efficacy IA changed from 75% to 48% and thus hazard ratio threshold and alpha had to be changed. Since the futility analysis was already conducted under the design of protocol version 00 (40% information fraction out of 180 events), no changes were made to the threshold for declaring futility or its calculation.

In addition, editorial changes and text corrections were made for clarification, where required.

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 do NOT affect the Informed Consent.

[redacted]

Amendment 2 (14-Jul-2021)

Amendment rationale

As of the release of this amendment, approximately 324 subjects have been randomized in this trial.

The main purpose of this amendment is to clarify inclusion criterion #3 related to MDS/CMML-2 status of the patient and exclusion criterion #9 related to myelofibrosis. It was clarified that the IPSS-R score used for MDS patients in this study is solely based on the publication from Greenberg et al 2012 to ensure consistency across the participating sites. For CMML-2, it was clarified that in alignment with the WHO classification 2016 (Arber et al 2016), the diagnosis of CMML-2 contains the presence of monocytosis ≥ 1 $x10^9$/L and monocytes accounting for ≥ 10% of the WBC differential count. The requirement of WBC < 13 $x10^9$/L applies to the time of initial diagnosis; the WBC value may be higher at time of randomization. Exclusion criterion #9 has been updated to clarify that patients with grade 1 myelofibrosis without symptoms of concurrent myeloproliferative neoplasm can be enrolled. Fibrosis is often seen in MDS patients and fibrosis grade 0 and 1 does not affect overall survival (Ramos et al 2016).

Furthermore, new Novartis standard language, referred to as disruption proofing language, has been added to specify trial conduct during public health emergencies. The added language addresses study participant safety and trial integrity. In case subjects cannot come to the site during the follow-up period to complete the PROs at site, an alternative way of completion was included in order to minimize the risk of missing assessments for the key secondary objectives. In addition, guidance was added about PRO collection for illiterate subjects.

Additional guidance for COVID-19 vaccinations was added to avoid overlapping adverse events with study treatment, and several updates were made to clarify the visit windows in case of delay of administration of study treatment and time windows for certain assessments.

Lastly, the definition of withdrawal of consent and management of biological samples was updated as per latest protocol template.

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.

- Updated glossary of terms and list of abbreviations related to changes in other sections of the document
- Section 4.7 (Rationale for Public Health Emergency mitigation procedures) added
- Section 5.1: Inclusion criterion #3 updated to highlight that the IPSS-R score for MDS used in this study is solely based on the publication from Greenberg et al 2012. For CMML-2, it was clarified that diagnosis per WHO classification 2016 contains the presence of monocytosis ≥ 1 $x10^9$/L and monocytes accounting for ≥ 10% of the WBC differential count, and the requirement of WBC < 13 $x10^9$/L applies to the time of initial diagnosis

[redacted]

- Section 5.2: Exclusion criterion #9 updated to myelofibrosis grade 2 or higher. Patients with myelofibrosis grade 1 without symptoms of concurrent myeloproliferative neoplasm can be enrolled into the study.
- Section 6.1.1 and Section 6.7.2: Duration of administration of MBG453 or placebo specified to be preferably over 30 minutes, with a maximum administration time of 2 hours
- Section 6.2.1: Duration for recording of concomitant medications during follow-up phase updated. Clarification added that G-CSF is also allowed for prophylaxis but should not be given within 2 weeks before response assessment.
- Section 6.2.2: Clarification added for the timing of vaccination against COVID-19 in relation to the study treatment and for prophylactic G-CSF use. Corticosteroids should be tapered to 10 mg/day or less before the start of the next treatment cycle.
- Section 6.5.1: Clarification added that interruption of study treatment and delay of cycle start for 56 consecutive days does not necessarily lead to permanent discontinuation of the subject. Exceptions may be granted based on discussions with study team.
- Section 7: Remote ICF procedure allowed in case of public health emergency
- Section 8: Coagulation testing was added into the list of assessments which do not need to be repeated at C1D1 if done within 7 days of randomization. Visit window for bone marrow and PRO assessments was corrected to clarify that these assessments have to be done before administration of study treatment at the corresponding visit. Additional guidance was added for time windows for assessments in case of delay of administration of study treatment. In case of public health emergency, the option to perform some assessments remotely was added.
- Table 8-1: Clarified that efficacy peripheral blood collection includes conducting pathology assessment of this sample
- Section 8.2: Reference to IPSS-R score used in this study added. Clarification added that subjects should not receive blood transfusion for at least 7 days before the blood samples for randomization are collected. Clarification added on cytogenetics and blood smears.
- Table 8-5: Definition for blast in MDS/CMML-2 added
- Section 8.4.1 and Section 8.4.3: updated to allow alternative local labs and remote urine pregnancy testing in case of public health emergency
- Section 8.4.2: Number of ECG reads clarified in case of a safety finding
- Section 8.5.1.1: Alternative way completion of PROs during follow-up period added. Guidance added about PRO collection for illiterate subjects and during public health emergency situations
- Section 8.5.2: Update of target population for extensive PK sampling in Chinese subjects
- Table 8-7 and Table 8-8: Time window for pre-dose PK/PD/IG sample extended to up to 2 hours on Day 8 when azacitidine and MBG453/placebo are administered on the same day
- Section 9.1.2: Definition of withdrawal of consent was updated and clarifications added about the management of biological samples; this change was also included as appropriate in Sections 3, 8.3.1, Section 9.1.1, Section 9.1.3 and Section 9.1.5
- Section 10.1.3: SAE reporting timeframe updated with additional instructions and clarification for randomized subjects who were not treated with study treatment

[redacted]

- Appendix 1 "Liver event and Laboratory trigger Definitions and Follow-up Requirements" was removed
- Appendix 2: Guidance regarding hepatitis B updated to clarify that it is sufficient to measure either HBsAG or HBV DNA and that the Novartis study team should be consulted if local management of hepatitis B differs from suggestions in the protocol

In addition, editorial changes and text corrections were made for clarification, where required.

IRBs/IECs

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

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

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

[redacted]

Amendment 1 (06-Aug-2020)

Amendment rationale

As of the release of this amendment, 13 subjects have been randomized 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 Section 8.3, 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. Lastly, additional PK samples will be collected in a subset of Chinese patients to obtain extensive PK profile in Chinese patient population.

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 intensive chemotherapy or stem cell transplantation updated. Key Exclusion criteria amended to exclude patients who received investigational treatment within 5 half-lives of this treatment.
- Section 3: Term ‘Post Trial Access (PTA)’ was introduced.
- Section 4.2 and Section 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 5.1: Inclusion criteria 5 and 6 were amended to specify that assessment of eligibility for intensive chemotherapy or stem cell transplantation will include individual clinical factors such as age, comorbidities and performance status.
- Section 5.2: Exclusion criterion 3 was amended to exclude also patients who received investigational treatment within 5 half-lives of this treatment. Wording of exclusion criterion 12b modified for more clarity. Exclusion criterion 14 was amended to exclude patients with history of prolongation or QTcF > 470 ms at screening from this trial.
- Section 6.1.5: 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. Clarification on post trial access (PTA) added.

[redacted]

- Section 6.1.5.1: Criteria for continuation of study treatment or components of study treatment beyond progression modified. Guidance for assessment of clinical benefit added.
- Section 6.5.1, 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 6.5.2.1: Time-point of PK sample clarified as part of the follow-up actions for potential drug-induced liver injury cases.
- Section 6.7.1.1: Clarification added that azacitidine can be administered outside of investigational site as per local regulations.
- Section 6.7.2: Wording updated to clarify that azacitidine dose and route of administration should be applied as per local package insert. Reference to the pharmacy manual was added for investigational drug handling instructions.
- 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.
- Section 8: Definition of time windows was amended for more clarity. Time window for ePRO assessments and for bone marrow samples at end of treatment was extended. Clarification added that safety follow-up visits at Day 90 and Day 150 can be performed via telephone call or onsite visits.
- Section 8, Table 8-1: List of cytokines was removed. Clarification added that efficacy bone marrow sample can be an aspirate and/or a biopsy sample.
- 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 8.3.1: 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 8.4.1, 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 8.5.2: Addition of extensive PK sampling in a subgroup of Chinese patients. Clarification added that PK, IG and sTIM-3 samples will be analyzed only in subjects receiving MBG453.
- Section 8.5.2.2: Additional details about immunogenicity testing method added
- [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 are met. Incorrect reference to section 6.1.4 was removed.
- Section 9.2: Updated wording for post trial access (PTA) added.

[redacted]

- Section 10.1.4: Clarification added on process to follow in case of pregnancy.
- Section 11.2: Additional information included about data tracked in the Interactive Response Technology (IRT) system.
- Section 12.5.1.1: Estimand definition and censoring rules for the analysis of time to definitive deterioration of fatigue were added.
- Section 12.5.1.5: Estimand definition were added for fatigue, physical and emotional function analyses.
- Section 12.5.2: Clarification on response rate subgroup analyses was added and transfusion independence definition was updated as per Table 8-2.
- Section 12.5.4: Description of noncompartmental PK parameters added for analysis of additional PK samples collected in a subset of Chinese patients
- [redacted]
- [redacted]
- Section 16.4, Appendix 4: Clarification added that the futility boundary is "non-binding".

In addition, editorial changes and text corrections were made for clarification, where required.

IRBs/IECs

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Protocol summary

Protocol number	CMBG453B12301
Full Title	A randomized, double-blind, placebo-controlled phase III multi-center study of azacitidine with or without MBG453 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)
Brief title	Study of efficacy and safety of MBG453 in combination with azacitidine in subjects with intermediate, high or very high risk myelodysplastic syndrome (MDS) as per IPSS-R, or Chronic Myelomonocytic Leukemia-2 (CMML-2)
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Biological
Study type	Interventional
Purpose and rationale	The anti-TIM-3 monoclonal antibody MBG453 is a novel immunotherapeutic agent with promising activity in AML and MDS. The purpose of the current study is to assess clinical effects of MBG453 in combination with azacitidine in adult subjects with IPSS-R intermediate, high, very high risk MDS and CMML-2. The justification for a double-blind randomized placebo-controlled trial is to determine the efficacy of adding MBG453 to azacitidine on the primary efficacy endpoint (Overall survival).
Primary Objective(s)	The primary objective of this study is to compare overall survival (OS) in the MBG453 plus azacitidine arm versus placebo plus azacitidine arm where OS is the time from randomization until death due to any cause. If the subject is not known to have died, then OS will be censored at the latest date the subject was known to be alive (on or before the cut-off date).
Secondary Objectives	Key secondary objectives • To compare time to definitive deterioration of fatigue in the MBG453 plus azacitidine arm versus placebo plus azacitidine arm as measured by FACIT-Fatigue • To compare RBC transfusion-free intervals in the MBG453 plus azacitidine arm versus placebo plus azacitidine arm • To compare improvement of fatigue in the MBG453 plus azacitidine arm versus placebo plus azacitidine arm using FACIT-Fatigue • To compare improvement of physical functioning in the MBG453 plus azacitidine arm versus placebo plus azacitidine arm using EORTC QLQ-C30 • To compare improvement of emotional functioning in the MBG453 plus azacitidine arm versus placebo plus azacitidine arm using EORTC QLQ-C30 Secondary objectives • To assess response rate in each treatment arm as per investigator assessment • To assess PFS in each treatment arm, including transformation to acute leukemia per WHO 2016 classification, relapse from complete remission (CR) according to IWG-MDS or death due to any cause as per investigator assessment • To assess Leukemia-free survival in each treatment arm • To assess the safety profile of MBG453 when given in combination with azacitidine • To assess the improvement in RBC/Platelets transfusion independence in each treatment arm • To characterize the pharmacokinetics of MBG453 • To evaluate immunogenicity of MBG453 • To assess overall quality of life in each treatment arm by testing change from baseline in EQ-5D-5L scores and VAS scores over time and change from baseline to C12D1 of Global Health Status/QoL scores using EORTC QLQ-C30

Study design	This is a Phase III multi-center, randomized, two-arm parallel-group, double-blind, placebo-controlled study of MBG453 or placebo added to azacitidine in adult subjects with intermediate, high or very high risk myelodysplastic syndrome (MDS) as per IPSS-R, or Chronic Myelomonocytic Leukemia-2 (CMML-2). Subjects will be randomized in a 1:1 ratio to treatment arms as follow: • MBG453 800 mg IV Q4W plus azacitidine • Placebo IV Q4W plus azacitidine The randomization will be stratified into 4 groups: intermediate risk MDS, high risk MDS, very high risk MDS and CMML-2. All subjects who discontinued both study treatments will enter a long-term post-treatment follow-up including response and PRO assessments, and/or survival follow-up for up to 5 years after the last subject was randomized.
Study Population	The study population will include approximately 500 adult subjects with intermediate, high or very high risk (per IPSS-R prognostic risk categories) myelodysplastic syndrome or with Chronic Myelomonocytic Leukemia - 2 (CMML-2). These subjects have an indication for treatment with azacitidine in first-line setting and are not eligible for intensive chemotherapy or hematopoietic stem cell transplantation (HSCT) according to medical judgment by the investigator.

Key Inclusion 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 myelodysplastic syndrome (MDS) based on WHO 2016 classification (Arber et al 2016) by local investigator assessment with one of the following Prognostic Risk Categories, based on the revised International Prognostic Scoring System (IPSS-R) as per Greenberg et al 2012:
	  • Very high (> 6 points)
	  • High (> 4.5 - ≤ 6 points)
	  • Intermediate (> 3 - ≤ 4.5 points)
	  Or
	  Morphologically confirmed diagnosis of Chronic Myelomonocytic Leukemia -2 based on WHO 2016 classification (Arber et al 2016 - persistent PB monocytosis ≥ 1 x109/L and monocytes accounting for ≥ 10% of the WBC differential count) by local investigator assessment with WBC < 13 x 10^9/L at time of initial diagnosis
	• Indication for azacitidine treatment according to the investigator, based on local standard medical practice and institutional guidelines for treatment decisions
	• Not eligible at the time of screening for intensive chemotherapy according to the investigator, based on local standard medical practice and institutional guidelines for treatment decisions including assessment of individual clinical factors such as age, comorbidities and performance status (de Witte et al 2017)
	• Not eligible at the time of screening for hematopoietic stem cell transplantation (HSCT) according to the investigator, based on local standard medical practice and institutional guidelines for treatment decisions including assessment of individual clinical factors such as age, comorbidities, performance status, and donor availability (de Witte et al 2017)
	• Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2

Key Exclusion 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 is allowed except if the drug was administered within 4 months prior to randomization • Previous first-line treatment for intermediate, high, very high risk myelodysplastic syndromes (based on IPSS-R) or CMML-2 with any antineoplastic agents including for example chemotherapy, lenalidomide and hypomethylating agents (HMAs) such as decitabine or azacitidine. However, previous treatment with hydroxyurea or leukapheresis to reduce WBC count is allowed prior to randomization.

[redacted]

	• Investigational treatment received within 4 weeks or 5 half-lives of this investigational treatment, whatever is longer, prior to randomization. In case of a checkpoint inhibitor: a minimal interval of 4 months prior to randomization is necessary to allow randomization. • Subjects with Myelodysplastic syndrome (MDS) based on 2016 WHO classification (Arber et al 2016) with revised International Prognostic Scoring System (IPSS-R) ≤ 3 • Diagnosis of acute myeloid leukemia (AML) including acute promyelocytic leukemia and extra-medullary acute myeloid leukemia, primary or secondary myelofibrosis based on WHO 2016 classification (Arber et al 2016) • Diagnosis of therapy related myeloid neoplasms based on WHO 2016 classification (Arber et al 2016) • History of organ or allogeneic hematopoietic stem cell transplant
Study treatment	• MBG453 • Placebo • Azacitidine
Efficacy assessments	Information about survival will be collected during visits or via phone calls. During survival follow-up, the survival status of the subjects will be collected every 12 weeks. Disease response will be assessed locally by the investigator in all subjects (MDS and CMML-2) according to modified IWG criteria for MDS and WHO criteria (Cheson et al 2000, Cheson et al 2006, Arber et al 2016, Platzbecker et al 2019). Bone marrow aspirate (BMA)/biopsy and peripheral blood will be collected at screening and at regular intervals during treatment for assessment of disease. Subjects can be assessed for disease response at any time if clinically indicated, for example in case of suspicion of progression/relapse.
Pharmacokinetic assessments	Pharmacokinetic (PK) and immunogenicity (IG) samples will be obtained and evaluated in all subjects.
Key safety assessments	• Adverse event monitoring • Physical examination • Vital signs • ECOG PS • Monitoring of laboratory evaluations in blood and urine
Other assessments	Patient Reported Outcome assessments Subject-reported outcomes are planned using FACIT-fatigue score to assess patient reported fatigue and using the EORTC-QLQ-C30 and EQ-5D-5L scores to assess health-related quality of life, physical functioning, emotional functioning, disease symptoms, treatment-related side effects, global health status and utilities. [redacted]
Data analysis	Two interim analyses are planned, following a group sequential design: • A futility interim analysis will be performed after approximately 72 OS events (40% information fraction of 180 events as per protocol version 00) have been documented; • An efficacy interim analysis will be conducted when approximately 135 OS events (48% information fraction of 282 events as per protocol version 03) have been documented and when all subjects have been randomized.

[redacted]

	The primary analysis will be performed after approximately 282 OS events have been documented. The final analysis will occur at the end of study. If OS is statistically significant at the efficacy interim or at the primary analysis, the key secondary endpoints will be tested according to a specific testing strategy, and using a separate alpha spending function.
Key words	Phase III, MBG453, TIM-3, azacitidine, placebo, myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia-2 (CMML-2)

[redacted]

1 Introduction

1.1 Background

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

Myelodysplastic syndromes (MDS) correspond to a heterogeneous group of hematological malignancies that are associated with impaired bone marrow function, ineffective hematopoiesis, elevated bone marrow blasts and persistent peripheral blood cytopenias. Anemia is the most common peripheral blood abnormality reported in up to 85% of the patients at diagnosis (Steensma and Bennett 2006). As a result, most patients with MDS require red blood cell transfusion support at some time during their illness and some are transfusion-dependent from the time of diagnosis onward. Frequent use of transfusions may have a negative impact on survival in patients with high risk MDS engaged in routine care (Bell et al 2019). Additionally, anemia is frequently associated with fatigue which represents a significant concern for MDS patients impacting their quality of life (Heptinstall 2006). Cytogenetic abnormalities are frequently present at time of diagnosis and 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 median time until 25% of the MDS population developed AML 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), intensive chemotherapy or hypomethylating agents (HMAs; azacitidine and decitabine) (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 and may precede HSCT (Steensma 2018). HSCT remains the only curative option for MDS patients; however, many MDS patients are not candidates for HSCT (Passweg et al 2011; and see Section 4.1). In MDS patients without major co-morbidities who are classified as higher risk by IPSS-R , and who do not qualify for transplantation or intensive chemotherapy, HMAs are the first-line reference treatment. Azacitidine is the sole HMA which showed a prolongation of overall survival (OS) compared to conventional care regimens among patients with higher risk MDS [median OS,

[redacted]

24.5 versus 15 months, respectively, hazard ratio (HR) = 0.58; P < 0.0001] in the pivotal AZA001 randomized phase III trial (Fenaux et al 2009). Other controlled clinical trials reported median OS between 19 to 20 months in patients receiving azacitidine (Silverman et al 2002, Garcia-Manero et al 2018).

Azacitidine is generally administered for a minimum of 6 cycles (repeat cycle after 4 weeks), and continued for as long as the patient benefits. In clinical practice, azacitidine safety profile is mainly characterized by bone marrow suppression leading to dose-reduction or discontinuation of azacitidine, and supportive care, including blood transfusions, is frequently required during the course of the disease.

HMAs have improved outcomes for patients with intermediate/high risk/very high risk MDS; especially for patients who are not candidates for intensive chemotherapy regimens or HSCT. However, despite these improvements, prognosis for patients treated with HMAs remains poor. Median survival in intermediate, high and very high MDS patients are only 3 years, 1.6 years and < 1 year respectively (Greenberg et al 2012). Treatment failure, relapse and transformation to acute myeloid leukemia (AML) are frequent events. Once a patient with higher risk MDS has failed treatment with HMAs or transformation to AML has occurred, survival generally will not exceed 6 months. Thus, improved treatments in addition to HMAs and/or as an alternative to HMAs are urgently needed in this MDS patient population.

Occurring in 1 in 100,000 people each year, Chronic Myelomonocytic Leukemias correspond to the group of myeloid neoplasms according to the 2016 WHO classification (Arber et al 2016) with CMML-2 representing approximately 15-20% of the CMML population. Recently an international treatment guidelines was published by the European Hematology Association (EHA) (Itzykson et al 2018). EHA recommends to treat the myelodysplastic CMML-2 patients who are ineligible for transplantation with azacitidine.

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 T-cells in murine models of AML/MDS. In addition, there is evidence of pharmacodynamic activity and promise for checkpoint inhibition in MDS (Chen et al 2008, Zhang et al 2009, Yang et al 2014, Kong et al 2015, Ørskov et al 2015); however, it will be important to determine the ideal checkpoint inhibitor strategy and to consider combination therapies in order to optimize anti-tumor immunity. A few clinical trials have investigated immune checkpoint inhibitors in MDS and AML 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.

[redacted]

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 pre-treated (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; also known as hepatitis A virus cellular receptor 2) 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 overexpressed in bone marrow mononuclear cells and detection on blasts increases as MDS progresses. 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). MBG453 is a high-affinity, humanized anti-TIM-3 IgG4 monoclonal antibody which blocks the binding of TIM-3 to phosphatidylserine (PtdSer). First in human trials have shown that MBG453 can be safely administered with decitabine in MDS/AML subjects suggesting that MBG453 may be combined with hypomethylating agents (decitabine or azacitidine). Preliminary clinical activity has been observed particularly in high and very high risk MDS subjects (see clinical responses in Section 4.3.2).

There is an ongoing Phase II trial [CMBG453B12201] which is investigating MBG453 (CR and PFS as primary endpoints) in high risk MDS subjects. The trial is a double-blind, placebo-controlled study comparing MBG453 plus HMA versus placebo plus HMA.

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

[redacted]

1.2 Purpose

Prognosis is poor and life expectancy is short in intermediate, high, or very high risk MDS, and Chronic Myelomonocytic Leukemia 2 (CMML-2) patients treated with the current standard of care based on hypomethylating agents. Very few patients can benefit from a curative option with hematopoietic stem cell transplant (HSCT). HMAs represent the standard of care for the vast majority of patients who cannot receive HSCT or cannot be treated with intensive chemotherapy. Azacitidine is the sole HMA which demonstrated a survival gain over conventional care in higher risk MDS and CMML patients (Fenaux et al 2009). Complete remission is reported in a minority of patients treated by azacitidine alone, and clinical benefits of this drug are frequently transient and when it fails, treatment options in second line are limited.

The humanized anti-TIM-3 IgG4 monoclonal antibody MBG453 is a novel immunotherapeutic agent with promising activity seen in AML and MDS. The purpose of the current study is to assess clinical effects of MBG453 in combination with azacitidine in adult subjects with intermediate, high or very high risk MDS, and CMML-2. This randomized, two-arm parallel-group, double-blind, placebo-controlled study will compare MBG453 plus azacitidine or placebo plus azacitidine. Objectives and endpoints of the study are detailed in Section 2.

2 Objectives and endpoints

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

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To compare overall survival (OS) in the MBG453 plus azacitidine arm versus placebo plus azacitidine arm	• OS is the time from randomization until death due to any cause. If the subject is not known to have died, then OS will be censored at the latest date the subject was known to be alive (on or before cut-off date).
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• **Key Secondary Objective 1**: To compare time to definitive deterioration of fatigue in the MBG453 plus azacitidine arm versus placebo plus azacitidine arm	• Time from randomization to at least 3 points worsening from baseline in FACIT-fatigue scores with no subsequent improvement above this threshold or death due to any cause, whichever occurs first
• **Key Secondary Objective 2**: To compare RBC transfusion-free intervals in the MBG453 plus azacitidine arm versus placebo plus azacitidine arm	• Cumulative time of intervals with no evidence of RBC transfusion for at least 8 weeks at any point after randomization
• **Key Secondary Objective 3:** To compare improvement of fatigue in the MBG453 plus azacitidine arm versus placebo plus azacitidine arm	• Percent of subjects with at least 3 point confirmed improvement from baseline in FACIT-fatigue scores
• **Key Secondary Objective 4:** To compare improvement of physical functioning in the MBG453 plus azacitidine arm versus placebo plus azacitidine arm	• Percent of subjects with at least 10 point confirmed improvement from baseline in physical functioning using EORTC QLQ-C30

[redacted]

Objective(s)	Endpoint(s)
• **Key Secondary Objective 5**: To compare improvement of emotional functioning in the MBG453 plus azacitidine arm versus placebo plus azacitidine arm	• Percent of subjects with at least 10 point confirmed improvement from baseline in emotional functioning using EORTC QLQ-C30
• To assess response rate in each treatment arm	• Percentage of CR/mCR/PR/HI according to IWG-MDS as per investigator assessment - Percentage of SD according to IWG-MDS as per investigator assessment
• To assess PFS in each treatment arm	• Time from randomization to disease progression (including transformation to acute leukemia per WHO 2016 classification), relapse from complete remission (CR) according to IWG-MDS or death due to any cause, whichever occurs first, as per investigator assessment
• To assess Leukemia-free survival in each treatment arm	• Time from randomization to ≥ 20% blasts in bone marrow/peripheral blood (per WHO 2016 classification) or diagnosis of extramedullary acute leukemia, or death due to any cause
• To assess the safety profile of MBG453 when given in combination with azacitidine	• Incidence and severity of AEs and SAEs, changes in laboratory values and vital signs (per CTCAE version 5)
• To assess the improvement in RBC/Platelets transfusion independence in each treatment arm	• Number and percent of transfusion dependent subjects at baseline who become RBC/platelets transfusion independent after randomization as per IWG-MDS criteria
• To characterize the pharmacokinetics of MBG453	• Serum concentrations and pharmacokinetic parameters for MBG453
• To evaluate immunogenicity of MBG453	• Anti-drug Antibody (ADA) prevalence at baseline and ADA incidence on-treatment
• To assess overall quality of life in each treatment arm	• Change from baseline in EQ-5D-5L scores and VAS scores over time • Change from baseline to C12D1 of Global Health Status/QoL scores using EORTC QLQ-C30

[redacted]

[redacted]

3 Study design

The trial is a randomized, double-blind, placebo-controlled, multi-center phase III study of MBG453 or placebo added to azacitidine for the treatment of subjects with intermediate, high or very high risk MDS as per IPSS-R or with CMML-2.

Approximately 500 subjects will be randomized in a 1:1 ratio to receive azacitidine 75 mg/m^2, intravenous or subcutaneous, with or without MBG453 800 mg IV Q4W in 28-day treatment cycles (Figure 3-1). The randomization will be stratified into 4 groups: intermediate risk MDS, high risk MDS, very high risk MDS, and CMML-2. Crossover between treatment arms is not permitted at any time during the study.

Study treatment consists of cycles of MBG453 or placebo 800 mg IV Q4W administered on Day 8 of each cycle in combination with azacitidine administered to the subjects on days 1 to 7 (or on days 1 to 5 and days 8 and 9) of each cycle until treatment discontinuation (for treatment duration and reasons for discontinuation, please refer to Section 6.1.5 and Section 9.1.1). Treatment options and dosing information are provided in Section 6.1.1. The planned duration of a cycle is 28 days.

Subjects who become eligible for hematopoietic stem cell transplant (HSCT) or intensive chemotherapy at any time during the course of the study will be discontinued from study treatment.

All subjects must be followed for adverse events (AEs) after the last dose of azacitidine, MBG453 or placebo as indicated in Section 10.1.1. All women of child-bearing potential must be followed for pregnancy safety evaluations as per Table 8-1 and after last dose of azacitidine and MBG453/placebo as indicated in Section 10.1.4.

In addition, all subjects who discontinued both study treatments will enter a long-term post-treatment and/or survival follow-up. Subjects who discontinued both study treatments due to reasons other than progression, death, lost to follow-up, or withdrawal of consent/opposition to use data/biological samples will have hematology assessments, Patient Reported Outcomes (PRO) and response assessments at defined timepoints until documented disease progression, death, lost to follow-up, or withdrawal of consent/opposition to use data/biological samples (Figure 3-2). Survival and post-treatment follow-up data will be collected for up to 5 years after the last subject was randomized.

Regular safety reviews will be performed by an independent Data Monitoring Committee (DMC) throughout the study (see Section 10.2.1). Additionally, efficacy reviews will be performed by the DMC when pre-defined number of OS events are documented.

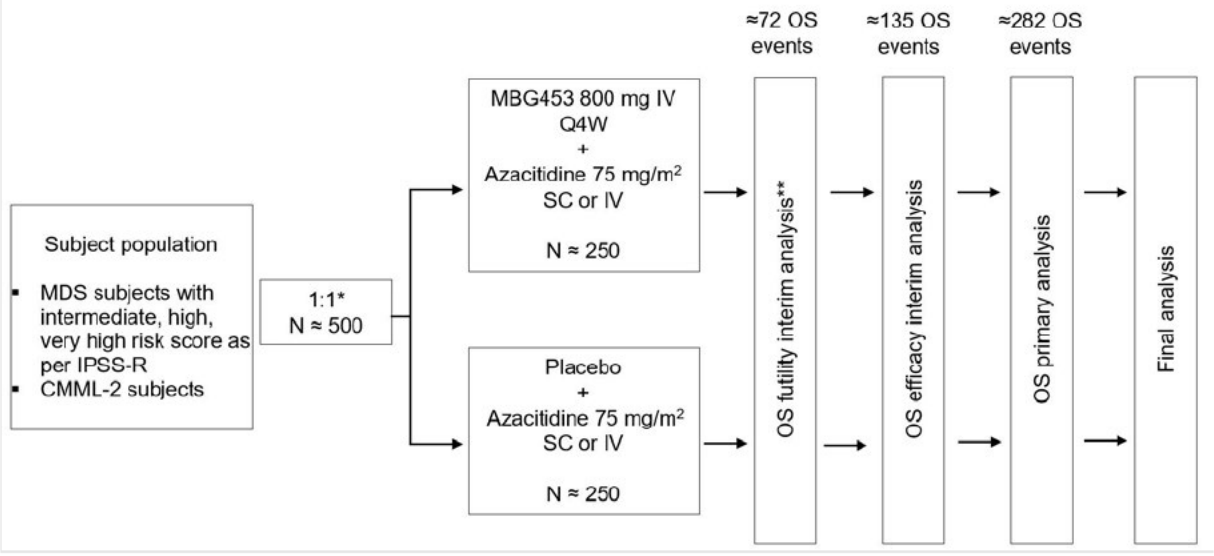
[redacted]

A futility interim analysis will be performed when approximately 40% of the 180 OS events as per protocol version 00 (approximately 72 OS events) have been observed, which is estimated approximately 20 months after the first subject randomized. At the time of the futility analysis, the OS data available from the parallel ongoing study [CMBG453B12201] will also be used to inform futility decision making. The decision criterion is to conclude futility if the probability of success (PoS) is less than 15% (refer to Section 12.7).

- An efficacy interim analysis will be conducted when approximately 48% of 282 OS events as per protocol version 03 (approximately 135 OS events) have been observed and when all subjects have been randomized. This is estimated approximately 22 months after first subject randomized.
- In the absence of early stopping, a primary analysis will be performed when approximately 282 OS events have been observed; this is expected approximately 44 months after first subject randomized (see Section 12.7). The primary analysis data will be summarized in the primary clinical study report (CSR).
- The final analysis will occur at the end of the study. All available data from all subjects up to this cut-off date will be analyzed and summarized in a final CSR.

The end of the study (Last Patient Last Visit) is defined as once all subjects discontinued study treatment and were transitioned to treatment outside the study which is targeted at the latest 5 years after the last subject was randomized. The Last Patient Last Visit will include all the required safety follow-up visits. At the end of the study, in alignment with local regulations, Post Trial Access (PTA) will be set up to provide MBG453 outside this study through an alternative setting to subjects who are receiving treatment with MBG453 and in the opinion of investigator are still deriving clinical benefit (see Section 9.2).

Figure 3-1 Study design

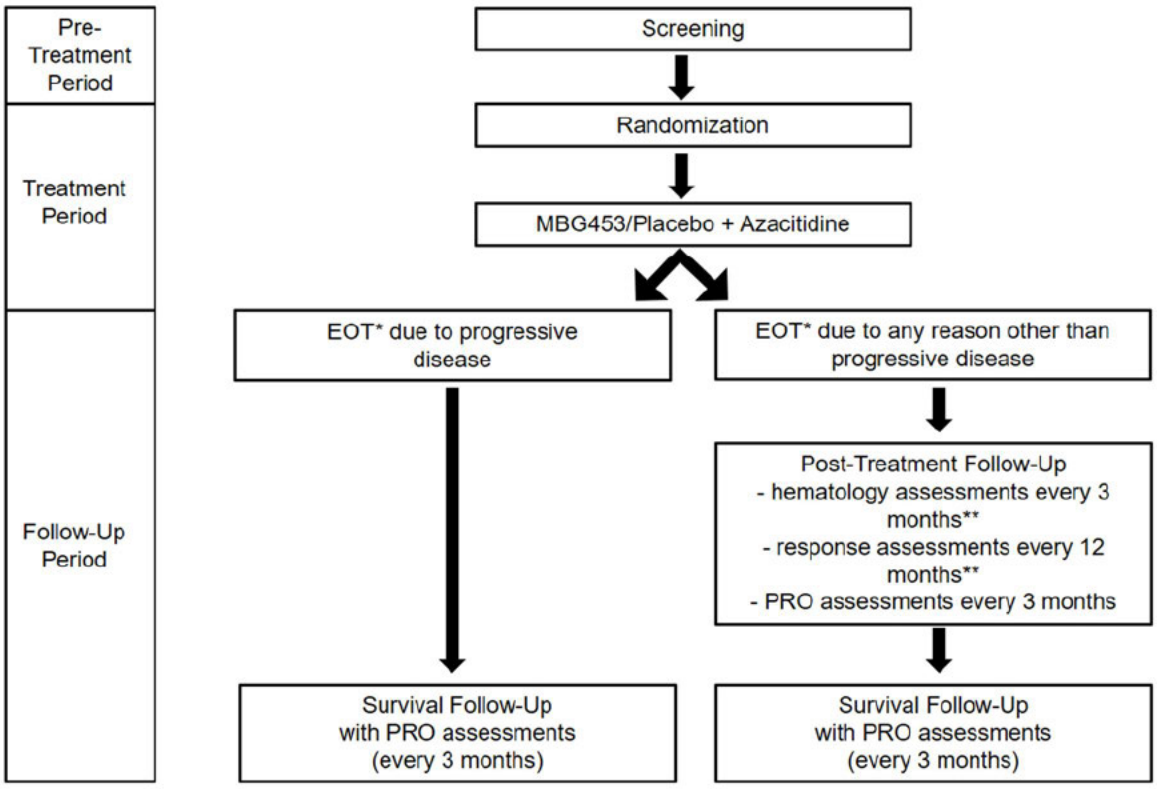


* The randomization will be stratified into 4 groups: intermediate risk MDS, high risk MDS, very high risk MDS and CMML-2.

[redacted]

** At futility analysis, the available data from phase II study [CMBG453B12201] will be used as prior information to calculate the probability of success

Figure 3-2 Study Flow



*EOT refers to the stop of both study treatments: MBG453/placebo plus azacitidine. All subjects must be followed for adverse events after the last dose of azacitidine and MBG453/placebo as per Section 10.1.1. For pregnancy follow-up please refer to Section 8.4.3.

**Hematology and/or response assessments can be done more often if clinically indicated.

4 Rationale

4.1 Rationale for study design

The justification for a double-blind, randomized, placebo-controlled trial is to determine the efficacy of adding MBG453 to azacitidine on the primary efficacy endpoint (Overall survival). The prospective, randomized, double-blind placebo-controlled design minimizes the risk of operational bias and provides a rigorous tool to examine cause-effect relationships between an intervention and outcome.

In this trial, subjects with higher risk MDS (defined as very high risk, high risk, intermediate risk), and subjects with CMML-2 will be enrolled. To take into account potential confounding factors, stratification will be used to balance allocation between treatment arms in terms of

[redacted]

clinical entities: CMML-2, MDS very high, MDS high and MDS intermediate risk according to IPSS-R score at baseline.

IPSS-R score at baseline for MDS subjects is a crucial clinical indicator in the sense that it will inform about the treatment outcomes and prognosis of each given subject. Each level of risk (intermediate/high/very high) is associated with a different estimated survival length and potential of leukemic transformation (see Section 1.1).

CMML-2 is considered as a distinct clinical entity according to WHO 2016 classification of myeloid neoplasms. Even though treatment paradigms and the clinical outcome in CMML-2 subjects are generally similar to that of higher risk MDS subjects, it is important to balance the treatment-arms regarding distribution of clinical entities by using stratification.

4.2 Rationale for dose/regimen and duration of treatment

The proposed MBG453 dose in the study is 800 mg Q4W based on data accumulated from two phase I studies: [CMBG453X2101] in solid tumor patients has a wide MBG453 dose range (single agent MBG453 from 80 to 1200 mg every 2 weeks (Q2W) or every 4 weeks (Q4W), with a lower 20 mg Q2W MBG453 dose additionally tested in combination with PDR001. Because of the data obtained in [CMBG453X2101], study [CPDR001X2105] started evaluating MBG453 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 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 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 subjects and CR or CRi in newly diagnosed AML subjects. Among responding higher-risk MDS subjects, 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 subjects with solid tumors have been treated with MBG453 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 subjects discontinued study treatment due to treatment-related AEs.

[redacted]

In study [CPDR001X2105], as of 26-Jul-2019, a total of 123 subjects with hematological malignancies have been treated with MBG453 as a single agent (n=26) or in combination with decitabine (n=81) or azacitidine (n=16). In the 26 subjects treated with MBG453 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 subjects (8%). All other adverse events attributed to study treatment were single occurrences. There were no DLTs during the first cycle. No subjects discontinued study treatment due to treatment-related AEs. In the 81 subjects treated with MBG453 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 subject experienced a DLT during the first 2 cycles, which consisted of hepatitis manifesting as Grade 3 ALT increase. One subject discontinued study treatment due to a treatment-related AE of possible hemophagocytic lymphohistiocytosis (HLH). In the 16 subjects treated with MBG453 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 subjects 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 Investigator's Brochure] for additional information of AEs reported in subjects with solid tumors or with hematologic malignancies treated with MBG453 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 concentration was fit to all subjects from both studies to the predicted TIM-3 occupancy in the bone marrow by making assumptions about MBG453 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 subjects 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

[redacted]

the receptor occupancy model; and the lack of a clear dose-response or exposure-response relationship for MBG453, 800 mg Q4W was selected as the dose regimen for this study.

4.3 Rationale for choice of combination drugs

4.3.1 Rationale for azacitidine

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

Treatment strategies for MDS are generally non-intensive and risk-adapted (by IPSS-R), ranging from watchful surveillance, iron chelation and growth factors to lenalidomide and HMA including azacitidine. Also, EHA recommends recently to treat myelodysplastic CMML-2 ineligible for allo HSCT with azacitidine (Itzykson et al 2018), see Section 1.1.

Higher risk MDS patients who are not transplant candidates are commonly treated with HMA therapy. HMAs represent the only approved therapeutic agents and constitute the current standard of 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.

Azacitidine is approved in the USA and in Europe for treating MDS and CMML. Azacitidine is the sole HMA which demonstrated a survival advantage over other treatment options in a randomized trial. 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. In this pivotal study a few CMML patients have been enrolled and a clinical benefit has been seen also in this patient population. Other clinical studies reported median OS ranging from 19 to 20 months in MDS patients (Garcia-Manero et al 2017, Silverman et al 2002).

Azacitidine is generally well tolerated and has a manageable toxicity profile (Derissen et al 2013). The most frequent toxicity is myelosuppression, primarily neutropenia and thrombocytopenia. Adverse events related to myelosuppression typically occur in the third week of the treatment cycle and subjects 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. In clinical trials, hematologic adverse events were more frequently observed during the first two treatment cycles, and 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 antidiarrheals.

Azacitidine regimens used in this trial 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 should be administered as per local standard practice (see Section 6.1.1).

[redacted]

4.3.2 Rationale for MBG453

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 subjects with solid tumors or hematological malignancies.

Abnormal upregulation of PD-L1, PD-L2, PD-1, and CTLA4 in CD34+ cells in MDS subjects 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 subjects treated with these agents alone or in combination to HMA (see Section 1.1).

Similarly to PD1 and CTLA4, MDS patients overexpress 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 is a high-affinity, humanized anti-TIM-3 IgG4 monoclonal antibody (stabilized hinge, S228P) which blocks the binding of TIM-3 to phosphatidylserine (PtdSer). Clinical trials of MBG453 are ongoing in solid tumors and hematological malignancies.

MBG453 as a single agent or in combination with decitabine or azacitidine was very well tolerated. Early data of MBG453 when combined with HMA indicate that most of the treatment-related AEs are anticipated in the context of MDS subjects receiving HMA (cytopenias, gastro-intestinal toxicities). Potential Immune-mediated AEs were generally low grades (grade 1/2) and manageable. For more details please refer to Section 4.2 and the [MBG453 Investigator's Brochure].

Preliminary efficacy data reported in study [CPDR001X2105] with higher-risk MDS subjects 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

[redacted]

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 months.

4.3.3 Rationale for combining MBG453 with azacitidine

Despite the fact that single-agent HMAs are available for the treatment of patients with higher risk MDS and CMML2, 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 rate of patients who could receive allo HSCT or as alternative treatment of cytarabine have been disappointing. In addition, many higher risk MDS and CMML2 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 1.1) strongly supports the evaluation of the novel anti-TIM-3 monoclonal antibody MBG453 combined with HMAs in myeloid neoplasms.

Preclinical data suggest that HMAs enhance checkpoint expression and that a synergistic response may be produced by using a checkpoint inhibitor and a hypomethylating agent; priming with HMA before giving MBG453.

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 checkpoint 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 higher-risk MDS subjects indicate that MBG453 plus decitabine combination is feasible, well tolerated and produces durable clinical responses (see Section 4.2 and Section 4.3.2). In [CPDR001X2105] study, a signal of a relevant clinical activity is being reported with high response rate, durable response and stable disease including in higher-risk MDS subjects who were treated (see above in Section 4.3.2).

Regarding safety data of MBG453, please refer to the [MBG453 Investigator's Brochure] for more details.

4.4 Purpose and timing of interim analyses

The statistical basis for claim of efficacy in favor of the MBG453 arm is based on statistical significance for OS as detailed in Section 12.4.2.

[redacted]

There will be two interim analysis:

- A futility interim analysis will be performed after approximately 72 OS events (40% information fraction out of 180 events as per protocol version 00) have been documented, with an option to stop for futility.
- An efficacy interim analysis will be performed after approximately 135 OS events (48% information fraction out of 282 events as per protocol version 03) have been documented and all patients randomized, with an option to stop for efficacy.

The primary OS analysis will be performed after approximately 282 OS events have been documented. The final analysis will occur at the end of study.

The timing of the interim, primary, and final OS analyses are detailed in Section 12.7. Figure 12-1 describes the study flow of the analyses.

4.5 Risks and benefits

The potential benefit of MBG453 combined with HMA in MDS is suggested by early efficacy results from the study [CPDR001X2105], which showed achievement of durable complete remission or bone marrow CR in higher-risk MDS patients receiving MBG453 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 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 subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring. The MBG453 dose established in other studies will be used for that trial, 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 subjects treated with immunologic agents, such as MBG453. 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 6.5.1 and Section 6.5.2). Additionally, general guidelines for non-hematologic non-immune-related toxicities that are clinically significant per investigator judgement and that are possibly attributable to the investigational drug are also provided (see Section 6.5.1).

Based on currently available data, there are no known significant overlapping toxicities between azacitidine and MBG453. However, there may be unforeseen risks from combining azacitidine with MBG453, which could be serious. In particular, since one focus of this study is to combine immunomodulatory agents in order to increase the antitumor immune response, there is the potential for increased toxicity secondary to increased release of cytokines which could result in cytokine release syndrome due to activation of T cells and macrophages. There may also be changes in the immune function that could lead to increased autoimmunity or risk of infection or risk of immune-related adverse events. All subjects enrolled will be monitored closely for

these potential toxicities. Furthermore, the protocol of the trial stipulates that a data monitoring committee (DMC) (Section 10.2.1) will meet regularly to review safety data.

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 subject 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 (Coronavirus disease of 2019) 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.

[redacted]

[redacted]

4.7 Rationale for Public Health Emergency mitigation 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

The study population will include approximately 500 adult subjects with intermediate, high or very high risk (per IPSS-R prognostic risk categories) myelodysplastic syndrome or with Chronic Myelomonocytic Leukemia - 2 (CMML-2). These subjects have an indication for treatment with azacitidine in first-line setting and are not eligible for intensive chemotherapy or HSCT according to medical judgment and local standard medical practice/institutional guidelines for treatment decisions.

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

5.1 Inclusion criteria

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

1. Signed informed consent must be obtained prior to participation in the study
2. Age ≥ 18 years at the date of signing the informed consent form (ICF)
3. Morphologically confirmed diagnosis of myelodysplastic syndrome (MDS) based on 2016 WHO classification (Arber et al 2016) by local investigator assessment with one of the

[redacted]

following Prognostic Risk Categories, based on the revised International Prognostic Scoring System (IPSS-R) as per Greenberg et al 2012:

- Very high (> 6 points)
- High (> 4.5 - ≤ 6 points)
- Intermediate (> 3 - ≤ 4.5 points)

OR

Morphologically confirmed diagnosis of Chronic Myelomonocytic Leukemia -2 based on WHO 2016 classification (Arber et al 2016 - persistent PB monocytosis ≥ 1 x10^9/L and monocytes accounting for ≥ 10% of the WBC differential count) by local investigator assessment with WBC < 13 x 10^9/L at time of initial diagnosis

4. Indication for azacitidine treatment according to the investigator, based on local standard medical practice and institutional guidelines for treatment decisions
5. Not eligible at time of screening for intensive chemotherapy according to the investigator, based on local standard medical practice and institutional guidelines for treatment decisions, including assessment of individual clinical factors such as age, comorbidities and performance status (de Witte et al 2017)
6. Not eligible at time of screening for hematopoietic stem-cell transplantation (HSCT) according to the investigator, based on local standard medical practice and institutional guidelines for treatment decisions, including assessment of individual clinical factors such as age, comorbidities, performance status, and donor availability (de Witte et al 2017)
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2
8. Estimated Glomerular Filtration Rate (eGFR) ≥ 30 mL/min/1.73m^2 (estimation based on Modification of Diet in Renal Disease (MDRD) formula, by local laboratory)
9. AST and ALT ≤ 3 × upper limit of normal (ULN)
10. Total bilirubin ≤ 1.5 × ULN (except in the setting of isolated Gilbert syndrome, where subjects may only be included with direct bilirubin ≤ 1.5 x ULN)
11. Subject is able to communicate with the investigator, and has the ability to comply with the requirements of the study procedures

5.2 Exclusion criteria

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

1. Prior exposure to TIM-3 directed therapy at any time. Prior therapy with immune checkpoint inhibitors (e.g, anti-CTLA4, anti-PD-1, anti-PD-L1, or anti-PD-L2), cancer vaccines is allowed except if the drug was administered within 4 months prior to randomization
2. Previous first-line treatment for intermediate, high, very high risk myelodysplastic syndromes (based on IPSS-R) or CMML with any antineoplastic agents including for example chemotherapy, lenalidomide and hypomethylating agents (HMAs) such as decitabine or azacitidine. However, previous treatment with hydroxyurea or leukapheresis to reduce WBC count is allowed prior to randomization.
3. Investigational treatment received within 4 weeks or 5 half-lives of this investigational treatment, whatever is longer, prior to randomization

   In case of a checkpoint inhibitor: a minimal interval of 4 months prior to randomization is necessary to allow randomization

[redacted]

4. Current use or use within 14 days prior to randomization 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. Live vaccine administered within 30 days prior to randomization
6. History of severe hypersensitivity reaction to any ingredients of the study treatments (azacitidine or MBG453) or their excipients, or to monoclonal antibodies
7. Subjects with Myelodysplastic syndrome (MDS) based on 2016 WHO classification (Arber et al 2016) with revised International Prognostic Scoring System (IPSS-R) ≤ 3
8. Diagnosis of acute myeloid leukemia (AML) including acute promyelocytic leukemia and extra-medullary acute myeloid leukemia based on WHO 2016 classification (Arber et al 2016)
9. Diagnosis of primary or secondary myelofibrosis grade 2 or higher based on WHO 2016 classification (Arber et al 2016). Patients with myelofibrosis grade 1 must not be enrolled if they have symptoms of concurrent myeloproliferative neoplasm (e.g. splenomegaly, constitutional symptoms, proliferative features and WBC not increased)
10. Diagnosis of therapy related myeloid neoplasms based on WHO 2016 classification (Arber et al 2016)
11. History of organ transplant or allogeneic hematopoietic stem cell transplant
12. Subjects with prior malignancy, **except:**
    a) subjects with history of lower risk MDS treated by supportive care (e.g. growth factors, TGF-beta agents) or untreated are eligible
    b) subjects with history of lower risk MDS who were treated adequately with lenalidomide and then failed are eligible
    c) subjects with history of adequately treated malignancy for whom no anticancer systemic therapy (namely chemotherapy, radiotherapy or surgery) is ongoing or required during the course of the study. Subjects who are receiving adjuvant therapy such as hormone therapy are eligible. However, subjects who developed therapy related neoplasm are not eligible (see exclusion 10).
13. Active autoimmune disease requiring systemic therapy (e.g. 10 mg/day prednisone or equivalent or any immunosuppressive therapy)
14. Any concurrent severe and/or uncontrolled medical condition including significant cardiac or cardiac repolarization abnormalities, history of QT prolongation or QTcF > 470 ms at screening. Subjects with active infection requiring parenteral antibacterial, antiviral or antifungal therapy which are controlled by adequate treatment are eligible.
15. Active Hepatitis B (HBV) or Hepatitis C (HCV) infection. Subjects whose disease is controlled under antiviral therapy should not be excluded. For additional guidance regarding serology for Hepatitis B, please refer to Section 16.2 (Appendix 2).
16. HIV infection not controlled by standard therapy and/or with known history of opportunistic infection.
17. Any other co-morbidity that, in the opinion of the investigator, predisposes the subject to high risk of noncompliance with the protocol

[redacted]

18. Sexually active males unwilling to use a condom during intercourse while taking azacitidine and for 3 months after stopping this treatment. 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 female partners will be instructed to use highly effective contraception.
19. Subject is pregnant or breastfeeding
20. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception while taking study treatment and for 3 months after the last dose of azacitidine (or as per the respective local label, whichever is longer) and 150 days after the last dose of MBG453 or placebo. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
    - Use of oral (estrogen and progesterone), injected or implanted 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 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 six 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.

    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 or placebo plus azacitidine.

The term “investigational drug” refers to the Novartis study drug, MBG453 or placebo.

[redacted]

A dose of 800 mg/8 ml MBG453 or placebo will be provided by Novartis and administered every 4 weeks (Q4W). Azacitidine will be administered in a standard dose of 75 mg/m^2 as per local clinical practice and locally available dose strengths.

For any component of the study treatment, all dosages prescribed and administered to the subject and all dose changes during the study (including the reason for change) must be recorded on the appropriate electronic Case Report Form (eCRF).

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
MBG453 400 mg/4 ml/Placebo	Concentrate for solution for infusion	Intravenous use	Double Blind; vial	Sponsor (global)
Azacitidine 100 mg (or other locally available dose strengths)	Lyophilized powder	Intravenous or subcutaneous	Open label; vial	Provided Locally

Azacitidine is considered as a Standard of Care in the population enrolled in this study and it should be administered according to standard local clinical practice. For further instructions, refer to Section 6.7.2. Azacitidine regimens used in this protocol were selected because these are the most studied regimen and recommended by international treatment guidelines (NCCN, ESMO, Steensma 2018).

MBG453 or placebo will be administered via i.v. infusion preferably over 30 minutes, with a maximum administration time of 2 hours. Further instructions for the preparation and administration of MBG453 or placebo are described in Section 6.7.2 and in the [CMBG453B12301 Pharmacy Manual].

6.1.2 Additional study treatments

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

6.1.3 Treatment arms/group

Subjects will be randomized in a 1:1 ratio to:

- MBG453 + azacitidine or
- Placebo + azacitidine

The randomization will be stratified into 4 groups:

- Intermediate risk MDS,
- High risk MDS,
- Very high risk MDS,
- CMML-2

[redacted]

6.1.4 Guidelines for continuation of treatment

The study treatment consists of azacitidine plus MBG453 or azacitidine plus placebo (Section 6.1.1).

Treatment will continue until a protocol-defined reason for discontinuation is met (Section 9.1).

Per protocol, dose modifications including interruptions for toxicities are permitted (Section 6.5.1, Section 6.5.2).

6.1.5 Treatment duration

Subjects will be treated until they experience progression of disease (including transformation to acute leukemia per WHO 2016 classification), experience unacceptable toxicity or discontinue the study treatment for other reasons (see Section 9.1.1 and Section 9.2). Continuation of study treatment beyond progression (excluding transformation to acute leukemia: continuation in this case is not possible) may be possible in selected subjects (Section 6.1.5.1).

Subjects may continue study treatment (azacitidine plus MBG453/placebo), azacitidine alone or MBG453/placebo alone if the investigator considers this is in the best interest for the subject. In this case, the subjects should continue to conduct the assessments outlined for treatment phase in Table 8-1.

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

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

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

6.1.5.1 Treatment beyond disease progression

Subjects receiving study treatment may enjoy clinical benefit despite initial evidence of disease progression. Subjects will be allowed to continue study treatment (azacitidine and MBG453/placebo), azacitidine alone, or MBG453/ placebo alone, beyond disease progression for up to the end of the study if all following criteria are met:

- 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)
- There is a clinical benefit observed per investigator assessment. The clinical benefit at the time of disease progression should consist of:

[redacted]

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 randomization

- No unacceptable toxicity is reported
- The subject continues to follow all protocol requirements

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

If the study treatment continues, the subjects should continue to perform all assessments for treatment 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 subject (e.g., such as anti-emetics, anti-diarrheal) is permitted (see Section 6.2.1.1), except when specifically prohibited (see Section 6.2.2). The subject must be told to notify the investigational site about any new medications he/she takes after the start of the study drug.

Subjects should not receive pre-medication to prevent infusion reaction before the first infusion of MBG453 or placebo. If a subject 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.

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 subject experiences a Grade 3 anaphylactic/anaphylactoid reaction, the investigational drug should be discontinued.

MBG453 or placebo should be administered in a facility equipped for cardiopulmonary resuscitation. Appropriate resuscitation equipment should be available and a physician readily available.

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

Relevant prior and all concomitant medication and non-drug therapies (including vitamin C intake for example) will be collected. Blood transfusions taken within 16 weeks before randomization and during the course of the study (including post-treatment/survival follow-up) should be recorded in the appropriate case report form (CRF). Information about antineoplastic therapies and HSCT after the end of study treatment should be collected during post-treatment and survival follow-up.

[redacted]

Concomitant medications/therapy do not need to be recorded after a patient started post-treatment antineoplastic medication. However, a concomitant medication/therapy given for an adverse event suspected to be related to study treatment will be recorded even if the patient has started the antineoplastic medication, for up to 150 days after discontinuation of MBG453/placebo.

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 randomizing a subject or allowing a new medication to be started. If the subject is already randomized, contact Novartis medical monitor to determine if the subject should continue participation in the study.

Supportive therapy including prophylactic antibiotic and antifungal treatments, transfusions, or any other supportive care 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 prophylaxis, infection or septicemia. Please adhere to Table 8-2 that no growth factors should be given prophylactically within 2 weeks before response assessments. Erythropoietin stimulating agents and thrombopoietic agents are prohibited during the course of the study (see Section 6.2.2).

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

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Anticoagulation therapy is permitted if the subjects are already at stable dose of warfarin or stable doses of low molecular weight heparin (LMWH) for > 2 weeks at time of first dose. International Normalized Ratio (INR) should be monitored as clinically indicated per investigator's discretion. Subjects 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, 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, since 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 or placebo.

6.2.2 Prohibited medication

During the course of the study, subjects 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 in the context of blood transfusion or replacement-dose

[redacted]

steroids in the setting of adrenal insufficiency or any transient exacerbation of other underlying diseases, as an example 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 start of the cycle. If more than 10 mg/day prednisone is used, study treatment (Azacitidine + MBG453/placebo) should be interrupted until the subject 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, unless these are attenuated vaccines, but should not be administered on the same day of study treatment administration to avoid potential overlapping adverse events.

Erythropoietin stimulating agents and thrombopoeitic 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 prophylaxis, infection or septicemia. Please adhere to Table 8-2 that no growth factors should be given prophylactically within 2 weeks before response assessments.

In addition, prohibited medication related to azacitidine will apply according to the locally approved product information.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.) that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it, so that each subject'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 subject the next sequential Subject No.

Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed unless the subject is re-screened. If the subject fails to be randomized or start treatment for any reason, the reason will be entered into the appropriate eCRF page, and the Interactive Response Technology (IRT) system should be notified as soon as possible. Re-screening is allowed once for subjects that were initially screen failures for any reason. All eligibility criteria must be re-checked and met prior to enrollment of the subject into the study. A new ICF will need to be signed if the investigator chooses to re-screen the subject. A new Subject No. should be assigned for all re-screened subjects.

6.3.2 Treatment assignment, randomization

In this randomized, placebo-controlled trial, subjects will be randomized in a 1:1 ratio to one of the two treatment arms (MBG453 + azacitidine or placebo + azacitidine) (Section 6.1).

[redacted]

At visit C1D1, following completion of screening procedure, all eligible subjects will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm. The randomization number will not be communicated to the investigator or his/her delegate.

MBG453/placebo will not be dispensed at this visit, the IRT will specify at C1D8 a unique medication number for the first package of MBG453 or placebo to be administered to the subject.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. Random permuted blocks scheme will be used for this study.

These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

Randomization will be stratified into 4 groups: intermediate risk MDS, high risk MDS, very high risk MDS and CMML-2 (for rationale for stratification, please refer to Section 4.1).

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

6.4 Treatment blinding

OS futility and all safety/efficacy interim analyses will be performed by an independent statistician and reviewed by a Data Monitoring Committee (DMC). Novartis clinical team, subjects, investigators and persons performing the assessments will remain blinded to the results of the analysis and the identity of the treatment from the time of randomization until primary analysis unless the DMC has determined that the study needs to be terminated due to any cause including safety reasons.

At the time of the efficacy interim analysis, if the OS is statistically significant, the Novartis clinical team will be unblinded. Subjects, investigators, site personnel, persons performing the assessments, will remain blinded to the results of the analysis and the identity of the treatment until the primary analysis.

Blinding will be ensured using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study with the following exceptions: Global Clinical Supply and PK analysts team (2) the identity of the treatments will be concealed by the use of study treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste, and odor.

[redacted]

The randomization codes associated with subjects from whom PK samples are taken will be disclosed to the PK analysts to facilitate the analysis of the PK samples. The PK analysts will keep the PK results confidential until the final database lock.

To limit the impact of unblinding on the scientific validity of the study results, individual subject unblinding is prohibited. Unblinding will only be permitted in the case of subject emergencies (Section 6.6.2), at the conclusion of the study and for regulatory reporting purposes.

6.5 Dose escalation and dose modification

Dose escalation is not applicable.

6.5.1 Dose modifications

For subjects who do not tolerate the protocol-specified dosing schedule, dose interruptions, and/or reductions are either recommended or mandated in order to allow subjects to continue the study treatment.

Dose modifications for azacitidine will be done according to local practice and country-specific drug label.

Dose modifications for MBG453 or placebo will be done according to ASCO guidelines on the management of immune-related AEs (Brahmer et al 2018). Additionally, a guidance indicated in Table 6-2 below provides instructions for infusion reactions, immune-related AEs not covered by ASCO guidelines and a general guideline for non-hematologic non-immune-related toxicities that are clinically significant per investigator judgment 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.

Deviations to dose interruptions, reductions and/or permanent discontinuations outlined in Table 6-2 are not allowed.

Dose modifications for MBG453 or placebo

(See Table 6-2 and refer to Brahmer et al 2018)

Administration of MBG453 or placebo 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 by the next planned treatment cycle. Dose reductions for MBG453 or placebo are not allowed; however, longer intervals for administration (Q8W instead of Q4W) are permitted in some clinical situations, as described in Table 6-2.

Overall, for adverse events of potential immune-related etiology (irAE) that do not recover to ≤ Grade 1 or baseline at a dose of immunosuppression of ≤ 10 mg/day prednisone or equivalent (or as indicated in Table 6-2) within 12 weeks after initiation of immunosuppressive therapy, MBG453 or placebo must be permanently discontinued.

[redacted]

Dose modifications for azacitidine

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

Permanent discontinuation of MBG453 or placebo and azacitidine

If the study treatment (i.e. MBG453 + azacitidine or placebo + azacitidine) 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, azacitidine and MBG453/placebo), the subject should be discontinued from study treatment. In exceptional cases this may be longer; please consult with the Novartis study team.

Permanent discontinuation of only one component MBG453/placebo or azacitidine

If **one component only** of the study treatment (azacitidine or MBG453/placebo) is discontinued for toxicities, then the treatment may continue with the other component of study treatment alone (MBG453 or placebo alone or azacitidine alone) as long as the subject benefits per investigator's judgment.

These dose changes must be recorded on the appropriate CRF.

Table 6-2 Criteria for dose interruption and re-initiation of MBG453 or placebo for adverse drug reactions

Worst toxicity CTCAE Grade V5.0	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/placebo
Adverse events thought to be immune-related AEs and not covered in the ASCO Guidelines for the management of immune-related adverse events in subjects treated with immune checkpoint inhibitor therapy (Brahmer et al 2018)	
Grade 1	No change. Continue MBG453/placebo at the same dose (800 mg) and schedule (Q4W)
Grade 2, or Grade 3 ≤ 7 days	Delay MBG453/placebo 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/placebo 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.

[redacted]

Worst toxicity CTCAE Grade V5.0	Dose Modifications
Grade 3 lasting ≥ 21 days Or Grade 4	Discontinue MBG453/placebo
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 azacitidine or the underlying MDS including its complications.	
Grade 1	No change. Continue MBG453/placebo at the same dose (800 mg) and schedule (Q4W)
Grade 2, or Grade 3 ≤ 7 days	Delay MBG453/placebo 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/placebo 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/placebo
All dose modifications should be based on the worst preceding toxicity. * Infusion related reaction or allergic reaction/anaphylaxis. See Section 6.2.1 for instructions regarding prophylaxis. ** Per investigator judgment	

6.5.2 Follow-up for toxicities

Subjects, whose treatment is interrupted or permanently discontinued due to an adverse event 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. If subjects experience a SAE or an AE leading to discontinuation of the study treatment, an unscheduled PK blood sample should be obtained as close as possible to the event occurrence.

For guidance on renal alert criteria, actions and events follow up, please refer to Section 16.1 (Appendix 1).

Immune-related AEs

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

An irAE is any clinically significant AE affecting any organ that is associated with study drug exposure, is consistent with an immune-mediated mechanism, and where alternative explanations have been investigated and ruled out or are considered to be unlikely. Serologic, histologic and immunological assessments should be performed as deemed appropriate by the Investigator, to verify the immune related nature of the AE. An empiric trial of corticosteroids may also contribute to understanding the etiology of a potential irAE. All subjects with signs or symptoms of irAEs should be monitored and managed following the ASCO Guidelines for the management of immune-related adverse events in subjects treated with immune checkpoint inhibitor therapy (Brahmer et al 2018). For irAEs not covered by ASCO guidelines, please refer to Table 6-2.

[redacted]

In case of a suspected irAE, the relevant immunological assessments (e.g. rheumatoid factor, anti-DNA Ab, etc.) should be performed. In case of toxicity suspected to be a cytokine release syndrome, the assessments outlined in Table 8-5 must be performed.

Please follow Section 8.5.2 for additional instructions regarding PK.

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 rare in MDS and no cases of TLS have been reported in the ongoing [CPDR001X2105] for MDS subjects receiving MBG453 in combination with HMA.

During this study, subjects 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, subjects 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 (eg, febuxostat), and increased oral/ i.v. hydration prior to treatment should be given in subjects with elevated uric acid or high tumor burden
  - Prompt supportive care in case of acute TLS (i.v. fluids and treatment with rasburicase as clinically indicated, when uric acid continues to rise despite allopurinol/febuxostat and fluids)
- **During a treatment cycle:**
  - Frequent monitoring of the following laboratory tests (per assessment cycle and as clinically indicated): potassium, phosphorus, calcium, creatinine, and uric acid
  - Encourage oral hydration

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

Laboratory tumor lysis syndrome

- Defined as two or more of the following values within three days before or in the days following initiation of a treatment cycle:
  - Uric acid $\geq$ 8 mg/dL or 25% increase from baseline
  - Potassium $\geq$ 6 mEq/L or 25% increase from baseline
  - Phosphorus $\geq$ 4.5 mg/dL or 25% increase from baseline
  - Calcium $\leq$ 7 mg/dL or 25% decrease from baseline

[redacted]

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

Subjects 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.

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

Guidelines for follow-up on potential DILI cases are described in Table 6-3 and Table 6-4.

Table 6-3 Follow-up of abnormal liver chemistry results

ALT	TBL	Liver Symptoms	Action
ALT increase without bilirubin increase:			
If normal at baseline: ALT > 3 x ULN	Normal For subjects 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 elevated at baseline: ALT > 2 x baseline or > 200 U/L (whichever occurs first)			
If normal at baseline: ALT > 5 x ULN for more than two weeks	Normal For subjects with Gilbert's syndrome: No change in baseline TBL	None	- Interrupt investigational drug - 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 elevated at baseline: ALT > 3 x baseline or > 300 U/L (whichever occurs first) for more than two weeks			
If normal at baseline: ALT > 8 x ULN	Normal	None	
ALT increase with bilirubin increase:			
If normal at baseline: ALT > 3 x ULN	TBL > 2 x ULN (or INR > 1.5)	None	

[redacted]

ALT	TBL	Liver Symptoms	Action
If elevated at baseline: ALT > 2 x baseline or > 200 U/L (whichever occurs first)	For subjects with Gilbert's syndrome: Doubling of direct bilirubin		
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 6-4 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, i.v. drug abuse, travel, work, alcohol intake, and full clinical examination for evidence of acute or chronic liver disease, cardiac disease and infection etc. should be performed.
2. Review of concomitant medications, including nonprescription medications and herbal and dietary supplement preparations, alcohol use, recreational drug use, special diets, and chemicals exposed to within one month of the onset of the liver injury.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. Obtain PK sample, as close as possible to last dose of MBG453/placebo, if PK analysis is performed in the study.
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.

6.5.2.2 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 potassium and magnesium levels for detecting hypokalemia, hypomagnesemia). If abnormal, correct abnormalities.
- Review concomitant medication use for possible causes for QT prolongation (refer to Crediblemeds). Record all concomitant medications in the appropriate eCRF page.
- Monitor ECG per the institutional standards.

[redacted]

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

IRT must be accessed to assign a medication (kit) number to the subjects every time MBG453 or placebo is to be administered. The date and time of all study treatment administrations (azacitidine and MBG453/placebo) during the study and any deviations from the protocol treatment schedule will be captured by the investigator staff and reviewed by field monitor on the appropriate study treatment dispensing form. Compliance with the study treatment will be assessed by the field monitor at each visit and information provided by the pharmacist or by the investigator. All study treatment dispensed, returned or destroyed as per local regulation must be recorded in the Drug Accountability Log.

Pharmacokinetic samples will be taken in all subjects as detailed in the pharmacokinetic Section 8.5.2.

All dosages for MBG453 or placebo as well as azacitidine prescribed to the subject 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

Emergency unblinding should only be undertaken for safety reasons essential for effective treatment of the patient. Blinding codes may also be broken after a patient discontinues treatment due to disease progression if deemed essential to allow the investigator to select the patient's next treatment regimen, and after discussion and agreement with the sponsor.

Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide:

- protocol number
- subject number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

[redacted]

Study treatment must be discontinued once emergency unblinding has occurred. The subject will have an End of Treatment (EOT) visit completed and will continue to be followed as specified in the protocol (Section 9.1.5 and Section 9.1.6).

6.7 Preparation and dispensation

Each study site will be supplied by Novartis with investigational drug (MBG453 or placebo) in packaging of identical appearance per product volume. A unique medication number is printed on the label of the investigational drug.

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

MBG453 or placebo will be administered i.v. Further instructions for the preparation and dispensation of MBG453 or placebo are described in the [CMBG453B12301 Pharmacy Manual].

Azacitidine will be sourced locally. For details on preparation, refer to the country-specific label instructions and/or azacitidine package insert.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure, or the locally approved product information. Clinical supplies are to be administered only in accordance with the protocol. Technical complaints are to be reported to the Quality Assurance at Novartis or the respective manufacturing company.

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 subject except for the medication number.

Study drug MBG453/placebo will be administered to the patient by the study site staff. Azacitidine will be administered per local country and 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. Administration of azacitidine at C1D1 must be done at the investigational site.

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.

[redacted]

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

6.7.1.2 Handling of additional treatment

Not applicable.

6.7.2 Instruction for prescribing and taking study treatment

Dose and treatment schedule of MBG453 or placebo as well as azacitidine is described in Table 6-5.

Table 6-5 Dose and treatment schedule

Investigational / Control Drug	Dose	Frequency and/or Regimen
MBG453 or placebo	800 mg	i.v. infusion over 30 minutes on Day 8
Azacitidine	75 mg/m^2	i.v. or subcutaneously on Day 1-7 or on Day 1-5, 8 and 9

Azacitidine should be administered according to local standard clinical practice. A standard dose of azacitidine (75mg/m^2) will be given subcutaneously or intravenously (see local azacitidine package insert) every day for seven consecutive days on days 1 to 7 out of a 28 day cycle, followed by MBG453 or placebo. In keeping with standard clinical practice, the alternative schedule of 75 mg/m^2 for five consecutive days on days 1 to 5, followed by a two day break, then two consecutive days on days 8 and 9 will alternatively be permitted (alternative schedule).

MBG453 or placebo infusions will be administered on day 8 out of a 28 day cycle. Refer to Table 6-1.

If the alternative schedule is selected for azacitadine by the investigator, azacitidine and MBG453 or placebo will be given on the same day 8. Azacitidine should be administered first, followed by MBG453 or placebo. Further instructions are described in the [CMBG453B12301 Pharmacy Manual].

MBG453 or placebo will be administered via i.v. infusion preferably over 30 minutes, with a maximum administration time of 2 hours. Further instructions for the preparation and dispensation of MBG453 or placebo are described in the [CMBG453B12301 Pharmacy Manual].

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

7 Informed consent procedures

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

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

[redacted]

his/her understanding. If the subject 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 subject source documents. The date when a subject'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 study drug can be found in the Investigator's Brochure (IB) for MBG453 and/or in the latest locally approved product information for azacitidine. This information will be included in the subject informed consent and should be discussed with the subject 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 subject.

As per Section 4.7, 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 Health Authority. Remote ICF process may also be used (if allowed by local Health Authority) for re-consenting subjects who are in the follow-up phase of the study.

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.).

The study includes the option for the subjects to continue MBG453 or placebo alone. The study also includes the option for the subjects to continue treatment with MBG453/placebo and azacitidine, azacitidine alone, MBG453/placebo alone beyond progression in selected subjects without acute leukemia (see Section 6.1.5.1).

In both options (continuation of MBG453/placebo 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.

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

cryopreservation. Female partners of male subjects will be instructed to use highly effective contraception methods.

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

8 Visit schedule and assessments

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

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). For screening assessments, please refer to Section 8.2.

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

During the course of the study, test and/or procedures should occur on schedule whenever possible. During the treatment phase a visit window of +/- 3 days is allowed (however the time window for bone marrow aspirate/biopsy and ePRO is - 7 days), during the post-treatment follow up phase and the survival follow-up a visit window of +/-14 days is allowed. In case the infusion of MBG453 or placebo or azacitidine 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 azacitidine to be administered on the same day as randomization. After C1D1, a window of +/- 3 days is allowed for treatment administration for reason other than toxicities. For adjustment of study treatment for toxicities, please refer to Section 6.5.1. For PK collection days, the windows for the PK sampling time are provided in Section 8.5.2.1.

Each treatment cycle is 28 days. Each cycle's Day 1 visit and corresponding assessments are determined by the first dose of Azacitidine for the cycle.

If administration of study treatment is delayed within the allowed window for reasons other than toxicities, the investigator should preferably shorten the current cycle to bring the next back to schedule if allowed by local standard practice.

Subjects who discontinue the study treatment for any reason should be scheduled for an end of treatment (EOT) visit as soon as possible (up to 7 days after discontinuation), 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). At this visit, all administered investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

All subjects receiving the study treatment must have safety evaluations for 30 days after the last dose of azacitidine, and 150 days after the last dose of MBG453 or placebo. In addition, a pregnancy test should be performed for women of child-bearing potential at timepoints described in Section 8.4.3. After the safety follow-up onsite visit on Day 30 (to allow for PK and IG sampling), subjects will be followed via telephone call or onsite visits for the Day 90 and Day 150. For the safety follow-up visits a visit window of +/- 3 days is allowed.

[redacted]

Post-treatment follow-up or survival follow-up start from end of treatment visit. For details, please refer to Section 8.3.1, Section 9.1.5 and 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 allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site 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. Screening, C1D1, efficacy/response assessments (bone marrow and PB smear), collection of PK/PD/IG [redacted] samples as well as administration of investigational drug always have to be conducted at the investigational site.

[redacted]

Table 8-1 Assessment Schedule

Period	**Screening**	**Treatment**																**EOT**
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) (28d)**		
Visit Name	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**EOT**
Days	**-28 to -1**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**-**
Informed consent	X																	
IRT Screening	X																	
IRT Randomization		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																	

[redacted]

Period	**Screening**	**Treatment**																**EOT**
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) (28d)**		
Visit Name	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**EOT**
Days	**-28 to -1**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**-**
Physical Examination	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Height	X																	
BSA (use height from screening)		X		X		X		X		X		X		X		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	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Chemistry	X	X		X		X		X		X		X		X		On cycle 9 and every 2 cycles thereafter		X
Coagulation	X	X		X		X		X		X		X		X		On cycle 9 and every 2 cycles thereafter		X
Thyroid function	X			X						X						On cycle 8 and every 3 cycles thereafter		X
Ferritin, iron, erythrocyte and serum folates, vitamin B12	X	If clinically indicated																

[redacted]

Period	**Screening**	**Treatment**																**EOT**
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) (28d)**		
Visit Name	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**EOT**
Days	**-28 to -1**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**-**
Vitamin C	X																	
hs-CRP	X																	
Cytokines	X	Anytime for a suspected cytokine release syndrome, immediately after the AE, and one week after occurrence of AE																
Virology hepatitis B and C	S	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																

[redacted]

Period	**Screening**	**Treatment**																**EOT**
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) (28d)**		
Visit Name	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**EOT**
Days	**-28 to -1**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**-**
Efficacy - Bone marrow aspirate and/or biopsy	X													X		On cycle 13 and every 12 cycles thereafter, and if clinically indicated		If clinically indicated
Efficacy - Peripheral blood collection and pathology	X													X		On cycle 13 and every 12 cycles thereafter, and if clinically indicated		If clinically indicated
Cytogenetics	X																	
Response assessment														X		On cycle 13 and every 12 cycles thereafter, and if clinically indicated		X
FACIT-Fatigue		X				At Cycle 3 Day 1, then every 2 cycles thereafter, and at time of EOT												
[redacted]																		
EORTC QLQ-C30		X														At Cycle 12 Day 1		

[redacted]

Period	**Screening**	**Treatment**																**EOT**
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) (28d)**		
Visit Name	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**EOT**
Days	**-28 to -1**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**-**
EORTC QLQ-C30 (only emotional and physical functioning domain items)						At Cycles 3 - 6 - 9 Day 1, then from cycle 15 every 3 cycles thereafter, and at time of EOT												
EQ5D-5L (including VAS)		X				At Cycle 3 Day 1, then every 3 cycles thereafter, and at time of EOT												

[redacted]

[redacted]

Period	**Screening**	**Treatment**																**EOT**
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) (28d)**		
Visit Name	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**EOT**
Days	**-28 to -1**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**-**
[redacted]																		
Blood sample for PK analysis			X		X		X		X				X				On cycles 9, 12 and every 6 cycles thereafter	X
Blood sample for IG analysis			X		X		X		X				X				On cycles 9, 12 and every 6 cycles thereafter	X
[redacted]																		

[redacted]

Period	**Screening**	**Treatment**																**EOT**
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) (28d)**		
Visit Name	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**EOT**
Days	**-28 to -1**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**-**
[redacted]																		
Azacitidine infusion		on Days 1- 7 of each cycle OR on Days 1-5 and then on Day 8 and Day 9: IV or SC75mg/m2																
MBG453/Placebo infusion		on Day 8 of each cycle: 800 mg IV Q4W																
IRT - Drug Dispensation MBG453/Placebo			X		X		X		X		X		X		X		X	
Adverse Events	X	Continuous																

[redacted]

Period	**Screening**	**Treatment**																**EOT**
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) (28d)**		
Visit Name	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**EOT**
Days	**-28 to -1**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**D1**	**D8**	**-**
Concomitant medications and medical procedures (including blood transfusions requirement)	Continuous																	
Antineoplastic therapies, HSCT and transfusions since discontinuation of study treatment																		
Disposition	X																	X
IRT Discontinuation																		X
Survival Follow up																		

[redacted]

Period	**Safety FU**			**Post- treatment FU**	**Survival**
Cycle					
Visit Name	**D30**	**D90**	**D150**	**Post Treatment Follow Up**	**Survival**
Days	**-**	**-**	**-**	**-**	**-**
Informed consent					
IRT Screening					
IRT Randomization					
Demography					
Inclusion / Exclusion criteria					
Medical history/current medical conditions					
Disease History					
Prior antineoplastic therapies					
Prior medications, surgery and medical procedures (including blood transfusions requirement)					
Physical Examination					
Vital Signs					
Body Height					
BSA (use height from screening)					
Body Weight					
ECOG PS					
12-Lead ECG (triplicates)					
Hematology				Every 12 weeks and if clinically indicated	
Chemistry					
Coagulation					
Thyroid function					
Ferritin, iron, erythrocyte and serum folates, vitamin B12					

[redacted]

Period	**Safety FU**			**Post- treatment FU**	**Survival**
Cycle					
Visit Name	**D30**	**D90**	**D150**	**Post Treatment Follow Up**	**Survival**
Days	**-**	**-**	**-**	**-**	**-**
Vitamin C					
hs-CRP					
Cytokines					
Virology hepatitis B and C					
HIV serology (only if required per local regulation)					
Serum Pregnancy Test (only women with child-bearing potential)			S		
Urine Pregnancy Test OR Serum Pregnancy Test (only women with child-bearing potential)	D30, D60, D90, D120 after the last dose of MBG453/placebo				
Urinalysis dipstick and sediment					
Efficacy - Bone marrow aspirate and/or biopsy				If clinically indicated (for example if progression or relapse is suspected)	
Efficacy - Peripheral blood collection and pathology				If clinically indicated (for example if progression or relapse is suspected)	
Cytogenetics					
Response assessment				If clinically indicated (for example if progression or relapse is suspected)	
FACIT-Fatigue				Every 12 weeks	
[redacted]					
EORTC QLQ-C30					
EORTC QLQ-C30 (only emotional and physical functioning domain items)				Every 12 weeks	
EQ5D-5L (including VAS)				Every 12 weeks	

[redacted]

Period	**Safety FU**			**Post- treatment FU**	**Survival**
Cycle					
Visit Name	**D30**	**D90**	**D150**	**Post Treatment Follow Up**	**Survival**
Days	**-**	**-**	**-**	**-**	**-**
[redacted]					
Blood sample for PK analysis	X		If visit is done at site		
Blood sample for IG analysis	X		If visit is done at site		
[redacted]					
Azacitidine infusion					
MBG453/Placebo infusion					
IRT - Drug Dispensation MBG453/Placebo					

[redacted]

Period	**Safety FU**			**Post- treatment FU**	**Survival**
Cycle					
Visit Name	**D30**	**D90**	**D150**	**Post Treatment Follow Up**	**Survival**
Days	**-**	**-**	**-**	**-**	**-**
Adverse Events	Continuous				
Concomitant medications and medical procedures (including blood transfusions requirement)	Continuous				
Antineoplastic therapies, HSCT and transfusions since discontinuation of study treatment	Continuous				
Disposition				X	
IRT Discontinuation					
Survival Follow up					Every 12 weeks
[X] Assessment to be recorded in the clinical database or received electronically from a vendor [S] Assessment to be recorded in the source documentation only					

[redacted]

8.1 Screening

All subjects must provide signed ICFs prior to performing any study specific procedures. Subjects 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 randomization (Table 8-1). Laboratory parameters may be retested within the 28-day screening period from the ICF signature if such parameters do not meet the eligibility criteria. If the repeat value remains outside of the specified ranges at the end of the screening period, the subject cannot be enrolled into the study and will be considered a screen failure.

A subject may only be re-screened once for the study. A new ICF will need to be signed if the investigator chooses to re-screen the subject. For re-screened subjects, a new Subject No. should be assigned, and all required screening activities must be performed when the subject is re-screened for participation in the study.

Bone marrow and peripheral blood pathology specimen (i.e. bone marrow aspirate slides, bone marrow biopsy block if applicable, peripheral blood smears) prepared locally for establishing the MDS or CMML-2 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 specimen may be performed, if deemed necessary. For China only: Storage of the above pathological samples in a Novartis designated laboratory will be performed, if adequate approval has been obtained from all relevant Chinese authorities.

If bone marrow results for diagnosis are available from a sample collected within 28 days prior to randomization, the procedure does not have to be repeated at screening, the results can be used for diagnosis and baseline. In such cases, when BM sample is not collected at screening for clinical diagnosis, [redacted]. Instead, a viable cryopreserved BMA sample collected prior signing the informed consent should be provided, if available, and, [redacted]

8.1.1 Eligibility screening

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

8.1.2 Information to be collected on screening failures

Subjects who signed an informed consent form and subsequently found to be ineligible prior to randomization 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 subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a serious adverse event during the screening phase (see SAE section for reporting details, Section 10.1.3). If the subject fails to be randomized, the IRT should be notified within 2 days of the screen fail that the subject was not randomized.

[redacted]

Subjects who are randomized and fail to start treatment are not considered screen failures but are considered early terminators of study treatment. The reason for early termination of the study treatment should be recorded on the appropriate eCRF, and the subjects should be followed up for efficacy/PRO and survival.

8.2 Subject demographics/other baseline characteristics

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

- Relevant medical history or current medical conditions
- Disease history, including date of diagnosis, confirmation of MDS diagnosis, IPSS-R risk classification for MDS subjects at time of screening (Greenberg et al 2012), confirmation of CMML-2 status for CMML subjects, prior antineoplastic therapies.
  Calculation of IPSS-R risk score for MDS subjects and confirmation of CMML-2 status for CMML subjects should be done based on the hematology values obtained at screening. Blood samples used for randomization should be done at least 7 days after blood transfusion (if subject's condition allows).
- Relevant prior and all concomitant medications and medical procedures
- Blood transfusion(s) **administered within 16 weeks** prior to randomization

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 and pulse and body temperature)
- Laboratory: blood samples should be collected for hematology, chemistry, coagulation, serum pregnancy test for women of child-bearing potential, virology hepatitis B and C, HIV serology (only if required per local regulation), cytokines and additional tests as indicated in Table 8-1 and Table 8-5. If multiple laboratory tests were performed during screening to confirm eligibility, the lab values closest to randomization should be used (last available values during screening).
- Peripheral blood smears for pathology will be assessed locally to establish the diagnosis.
- [redacted]
- Urinalysis dipstick and sediment
- Cardiovascular assessments (i.e., triplicate 12-lead local ECG)
- Bone marrow aspirate (BMA) or biopsy will be performed locally to establish the diagnosis. Cytogenetics from this bone marrow sample will be performed locally as per local standard. If a bone marrow aspirate or biopsy was conducted during the regular work-up of the subject and falls within 28 days prior to randomization (although prior to signing main study ICF), it may be considered as the baseline assessment for the study.
- [redacted]

[redacted]

[redacted]

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.

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

8.3 Efficacy

8.3.1 Efficacy assessments

Survival

Information about survival will be collected during visits or via phone calls, the frequency of collection will be every 12 weeks during the survival follow-up as described in Table 8-1 and in Section 3. A subject will be considered lost-to-follow up after 3 failed documented attempts of contact.

Hematological Response per modified IWG-MDS criteria

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

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

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

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

Response category	Definition[#]
Complete remission (CR)	**Bone marrow**: ≤ 5% blasts with normal maturation of all cell lineages.(Note: Persistence of dysplasia will be noted but does not preclude achievement of complete remission [CR])

[redacted]

Response category	Definition[#]
	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 subject 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 subjects 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 subject 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. *Subjects 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****

[redacted]

Response category	Definition[#]
	Occurrence of acute leukemia, or extramedullary leukemia per investigator's judgement
Modified Hematologic Improvement per IWG-MDS criteria (Cheson et al 2006)	
HI category	**Definition[#] (HI must last at least 8 weeks)**
Erythroid response (HI-E) (pretreatment*, <11 g/dL)	1. Hgb increase from baseline by ≥ 1.5 g/dL, in at least 2 consecutive Hgb measurements and maintained over at least 8 weeks 2. Relevant reduction from baseline of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pre-treatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hgb of < 9 g/dL pre-treatment will count in the RBC transfusion response evaluation.
Platelet response (HI-P) (pretreatment*, <100 x 10^9/L)	3. Absolute increase from baseline of ≥ 30 x 10^9/L for subjects starting with > 20 x 10^9/L platelets 4. Increase from baseline from < 20 x10^9/L to > 20 x10^9/L and by at least 100% for subjects starting with < 20 x 10^9/L platelets
Neutrophil response (HI-N) (pretreatment*, <1.0 x 10^9/L)	At least 100% increase and an absolute increase from baseline of > 0.5 x 10^9/L

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

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

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

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

Transfusions Status Definitions for RBC/platelets

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

Transfusion dependence

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

Transfusion independence:

1. At baseline: subjects having received 0 units of transfusion within the 8 consecutive weeks prior to baseline.
2. Post-baseline: subjects 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, subjects 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 subject has achieved a CR.

Bone marrow assessments will be performed at screening and pre-dose on C7D1 and C13D1. After C13D1, bone marrow assessments will be performed every 12 cycles (C25D1, C37D1, etc.) until end of treatment. Hematology assessments will be performed at screening, and pre-dose on D1 and D8 of each cycle until cycle 7 included; and thereafter on D1 of each cycle until end of treatment.

Bone marrow and peripheral blood pathology specimens (i.e. bone marrow aspirate slides, bone marrow biopsy block if applicable, peripheral blood smears) prepared locally for the disease response assessment, should be sent to the Novartis designated central laboratory for storage. This includes specimens taken during the regular work-up of the subject and used as baseline

[redacted]

assessment for the study as mentioned in Section 8-2. A copy of the corresponding pathology reports should be collected and sent to the Novartis designated central laboratory for storage. Central morphology review of the pathology specimens may be performed, if deemed necessary. For China only: Storage of the above pathology specimens and reports in a Novartis designated laboratory will be performed, if adequate approval has been obtained from all relevant Chinese authorities.

Subjects who discontinue treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent/opposition to use data/biological samples, will enter the post-treatment follow-up phase. Hematology assessments must continue to be performed every 12 weeks, and bone marrow assessments should be done if clinically indicated (for example if progression or relapse is suspected) per Table 8-1. Transfusion information will be collected during post-treatment follow-up phase.

The post-treatment follow-up period will last until subject's documented disease progression (per IWG criteria Table 8-2), death, lost to follow-up, or withdrawal of consent/opposition to use data/biological samples, or the end of the study whichever comes first.

All randomized subjects have to be followed for efficacy, regardless whether treatment received or not.

8.3.2 Appropriateness of efficacy assessments

Overall Survival is the primary endpoint of the study and will be assessed according to a standard methodology. Hematological responses based on assessment of bone marrow, peripheral blood and history of blood transfusions are standard for the indications (MDS, CMML-2) investigated in this study and recommended by international treatment guidelines (IWG-MDS).

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.

[redacted]

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. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A complete physical examination is required at D1 of each cycle. At D8, an abbreviated examination can be done at investigator's discretion. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF 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 at screening and at subsequent time points as specified in Table 8-1.

Performance status:

The Eastern Cooperative Oncology Group/World Health Organization Performance Status (ECOG/WHO PS) scale will be used as described in Table 8-4.

Table 8-4 ECOG performance status

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

8.4.1 Laboratory evaluations

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

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 subject's eligibility.

If participants cannot visit the site for protocol specified safety lab assessments due to public health emergency, an alternative lab (local) collection site may be used. The local lab must

[redacted]

provide Novartis with a copy of the certification and a tabulation of the normal ranges and units for all local laboratories used 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 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.

Table 8-5 Clinical laboratory parameters collection plan

Test Category	Local/Central	Test Name
Hematology[1]	Local	Hematocrit, Hemoglobin, MCH, MCHC, MCV, Platelets, Red blood cells, White blood cells, RBC Morphology, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands), Blasts[7], Other (absolute value preferred, percentages are acceptable)
Chemistry	Local	Albumin, ALP, 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[3]
Virology[2]	Local	HBsAg, HBcAb, HBV DNA (in subjects positive for HBcAb), HCV RNA (Polymerase chain reaction) HIV (Only if required by local regulation)
Coagulation	Local	International normalized ratio (INR), Activated partial thromboplastin time (aPTT)
Cytokines	Central	IFN-γ, IL-6, IL-1 β, TNF-α, IL-10, IL-2, IL-4, IL12-p70, IL-13, IL-8
Urinalysis dipstick and sediment[2]	Local	Dipstick examination includes specific gravity, pH, glucose, protein, blood, bilirubin, ketones and WBC as clinically indicated
Pregnancy Test[2]	Local	Serum / Urine pregnancy test (refer to Section 8.4.3)
Additional tests	Local	Ferritin, iron, vitamin B12, erythrocyte and serum folates[4], TSH[5], Free T3 and/or Free T4
	Central	hs-CRP (high-sensitivity C-reactive protein), vitamin C, glutamate dehydrogenase[6]

[1] During treatment, hematology should be performed at every visit and if clinically indicated at any time during the study. During post-treatment follow-up, hematology should be performed every 12 weeks and if clinically indicated at any time during the study
[2] Virology, urinalysis and pregnancy test will only be reported in the source documentation.
[3] If Troponin T is not available, Troponin I may be performed. Troponin T can be assessed centrally in China, if not feasible locally.
[4] Preferred method is erythrocyte folate but in case it is not available, then serum should be performed. However, every effort should be made to perform both tests.
[5] During treatment: TSH at timepoints indicated in Table 8-1 and as clinically indicated. If TSH is abnormal, then test free-T3 and/or free-T4
[6] Test to be done in case of a suspicion of DILI, please refer to Table 6-3.
[7] As blasts in MDS/CMML-2 are counted: myeloblasts, monoblasts and promonocytes

8.4.2 Local 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

[redacted]

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 randomizing the subject 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.

ECGs should always be performed in triplicate to confirm a 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 6.5.2.2.

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 subjects

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

A serum pregnancy test (serum ß-HCG) must be performed at screening and at EOT visit. The test needs to be repeated at C1D1 before start of study treatment unless a serum pregnancy test had been performed within 72 hours before 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).

Additionally, during the safety follow up, women of child-bearing potential will be tested monthly with urine or serum pregnancy tests up to D90 after the last dose of azacitidine. They will also be tested monthly with urine or serum pregnancy tests up to D120 after the last dose of MBG453/placebo, and a serum pregnancy test should be performed on D150 after the last dose of MBG453/placebo.

If the subject is not coming to the clinic during the safety follow-up period or during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or

[redacted]

natural disaster, that limits or prevents on-site study visits, the urine 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.

Serum and/or urine pregnancy test will be performed only for women of child-bearing potential.

Women of child-bearing potential should employ the use of highly effective contraception during study treatment, for 3 months after the last dose of azacitidine (or as per their respective local labels, whichever is longer) and for 150 days after the last dose of MBG453 or placebo. 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 subject regardless of reported reproductive/menopausal status at screening/baseline.

Male subjects

A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner while taking azacitidine and for 3 months after stopping these drugs. In addition, male participants should not donate sperm for the time period specified above, and female partners will be instructed to use highly effective contraception.

Prior to starting treatment, male subjects are advised to seek consultation on sperm storage and female subjects 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 6.5.2 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 Appropriateness of safety measurements

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

[redacted]

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

8.5.1.1 Patient reported outcomes (PRO)

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

The European Organization for Research and Treatment of Cancer's core quality of life questionnaire (EORTC-QLQ-C30) and EuroQol Five Dimensions Questionnaire (EQ-5D-5L) will be administered during the course of the study to evaluate patient reported health-related quality-of-life (QoL), physical functioning, emotional functioning, disease symptoms, treatment-related side effects, global health status, and utilities.

The EORTC-QLQ-C30 is a 30-item PRO questionnaire developed to assess the quality of life of cancer patients and is composed of both multi- and single-item scales. The questionnaire consists of five functional scales, several symptom scales, and one global health status scale (Aaronson et al 1993).

The EQ-5D-5L is a six item, generic QoL questionnaire intended to provide clinical and economic utility evaluations of health care via the assessment of five dimensions of health: mobility (walking), self-care (washing and dressing), usual activities (e.g., work, study, housework, family or leisure activities), pain/discomfort, and anxiety/depression (Herdman et al 2011). In addition, one item asks respondents to rate their overall health on a visual analog scale (VAS). The EQ-5D-5L total score will be used to derive utilities for cost effectiveness analyses as needed for specific countries HTAs (Health Technology Assessment bodies).

[redacted]

[redacted]

All PRO questionnaires will be administered at time-points indicated in Table 8-1.

During post-treatment follow-up and survival follow-up period, FACIT-Fatigue, EORTC-QLQ-C30 physical functioning and emotional functioning domains and EQ-5D-5L will be administered as well as indicated in Table 8-1. During the post-treatment and survival follow-up period every effort should be made to have PROs completed by the subjects at the site. If not possible, an alternative way of completing the PROs electronically at home may be used.

All questionnaires should be administered in the language most familiar to the subject at the beginning of the scheduled visits prior to any interaction with the study personnel including any tests, treatments or receipt of results from any tests to avoid biasing the subject's perspective. At baseline, the questionnaire(s) will be applied prior to randomization. This is to avoid potentially biasing subjects or their responses to study questionnaires. Please refer to the study ePRO manual for detailed instructions for completion and handling of the ePROs.

Illiterate subjects who are not able to respond to the ePROs should have an interviewer (preferably a study nurse, or investigator or another health professional unrelated to the subject) who will read the questions aloud and complete the response as reported by the subject. The interviewer must not influence patient responses and should be specifically instructed on such cases to avoid interviewer-based bias.

PRO source data will be generated directly electronically. Completed questionnaire(s) may be made accessible to the study doctor/study personnel to enable to review them and act upon the responses according to their local practice.

The PRO measure(s) should be completed in the order reported in the ePRO manual.

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that prevents on-site study visits, PRO data may be collected remotely (e.g. web portal, telephone interviews) as a back-up solution depending on local regulations, technical capabilities, and following applicable training in the required process.

Scoring of PRO data and methods for handling of missing items will be handled according to the scoring manual and user guide for each respective subject questionnaire (Fayers 2001 and VanReenen M and Janssen 2015).

[redacted]

[redacted]

8.5.2 Pharmacokinetics

MBG453 pharmacokinetic (PK), Immunogenicity (IG) [redacted] samples will be obtained and evaluated in all subjects [redacted] Extensive PK sampling will be collected in a subgroup of Chinese patients (at least 30 patients treated in China). Please refer to Table 8-7 and Table 8-8 (PK subgroup) for details on PK, IG [redacted] sample collections.

If subjects experience a SAE or an AE leading to discontinuation of the study treatment, an unscheduled PK blood sample should be obtained as close as possible to the event occurrence. The date and time of the last dose and the time of PK blood draw should be recorded. If subjects experience suspected immunologically related AE such as infusion-related reaction, hypersensitivity, cytokine release syndrome and anaphylaxis, an unscheduled IG blood sample should be obtained as close as possible to the event occurrence. The date and time of the last dose and the time of blood draw should be recorded. An unscheduled PK and IG sample should also be taken at time of confirmed disease progression.

[redacted]

8.5.2.1 Pharmacokinetic blood collection and handling

MBG453 PK, IG [redacted] blood sampling schedule is outlined in Table 8-7 and Table 8-8. Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein opposite to the arm used for infusion. A single blood sample of approximately 5 mL will be collected. After clotting, the resulting serum will be separated in aliquots and will be stored frozen until analysis. The exact date and clock times of drug administration and blood draw for PK, [redacted] and IG assessment will be recorded on the appropriate eCRF.

After permanent discontinuation of MBG453 or placebo, the samples scheduled for pre-MBG453/placebo infusion and end of MBG453/placebo infusion (within 2 hours) should no longer be collected.

Refer to the [CMBG453B12301 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK, IG [redacted] samples.

[redacted]

PK, IG and sTIM-3 samples will be analyzed only in subjects receiving MBG453.

Table 8-7 Blood (serum) collection schedule for PK, IG [redacted]

Cycle	Day	Scheduled Time Point (h)*	PK sample	IG sample	[redacted]
1	1	Pre-Azacitidine infusion			X
1	8	Pre-MBG453/placebo infusion	X	X	X
1	8	End of MBG453/placebo infusion (within 2 hours)	X		
2	8	Pre-MBG453/placebo infusion	X	X	
3	8	Pre-MBG453/placebo infusion	X	X	X
3	8	End of MBG453/placebo infusion (within 2 hours)	X		X
4	8	Pre-MBG453/placebo infusion	X	X	
6	8	Pre-MBG453/placebo infusion	X	X	X
9	8	Pre-MBG453/placebo infusion	X	X	
Cycle 12 and every 6 cycles thereafter	8	Pre-MBG453/placebo infusion	X	X	
EOT	-	Anytime	X	X	
30 Day Follow up	-	Anytime	X	X	
150 Day Follow up**	-	Anytime	X	X	
Unscheduled***	-	Anytime	X	X	

*All predose samples should be collected within 30 min before the infusion begins. If Azacitidine and MBG453/placebo are administered on the same day, a time window of up to 2 hours before the infusion begins is acceptable for the pre-dose sample.

**150 Day Follow up samples can be collected at the investigator's discretion, if follow up visit is done at the site.

***Unscheduled PK and IG samples may be collected at any time if clinically indicated or at the Investigator's discretion. An unscheduled PK sample and IG sample should be collected upon confirmed disease progression.

[redacted]

Table 8-8 Blood (serum) collection schedule for PK subgroup (in China only)

Cycle	Day	Scheduled Time Point (h)*	PK sample	IG sample	[redacted]
1	1	Pre-Azacitidine infusion			X
1	8	Pre-MBG453/placebo infusion	X	X	X
1	8	End of MBG453/placebo infusion (within 2 hours)	X		
1	9	24 h after start of MBG453/placebo infusion (+/- 2h)	X		
1	15	168 h after start of MBG453/placebo infusion (+/- 8h)	X		
1	22	336 h after start of MBG453/placebo infusion (+/- 24h)	X		
2	8	Pre-MBG453/placebo infusion	X	X	
3	8	Pre-MBG453/placebo infusion	X	X	X
3	8	End of MBG453/placebo infusion (within 2 hours)	X		X
3	9	24 h after start of MBG453/placebo infusion (+/- 2h)	X		
3	15	168 h after start of MBG453/placebo infusion (+/- 8h)	X		
3	22	336 h after start of MBG453/placebo infusion (+/- 24h)	X		
4	8	Pre-MBG453/placebo infusion	X	X	
6	8	Pre-MBG453/placebo infusion	X	X	X
9	8	Pre-MBG453/placebo infusion	X	X	
Cycle 12 and every 6 cycles thereafter	8	Pre-MBG453/placebo infusion	X	X	
EOT	-	Anytime	X	X	
30 Day Follow up	-	Anytime	X	X	
150 Day Follow up**	-	Anytime	X	X	
Unscheduled***	-	Anytime	X	X	

*All predose samples should be collected within 30 min before the infusion begins. If Azacitidine and MBG453/placebo are administered on the same day, a time window of up to 2 hours before the infusion begins is acceptable for the pre-dose sample.

**150 Day Follow up samples can be collected at the investigator's discretion, if follow up visit is done at the site.

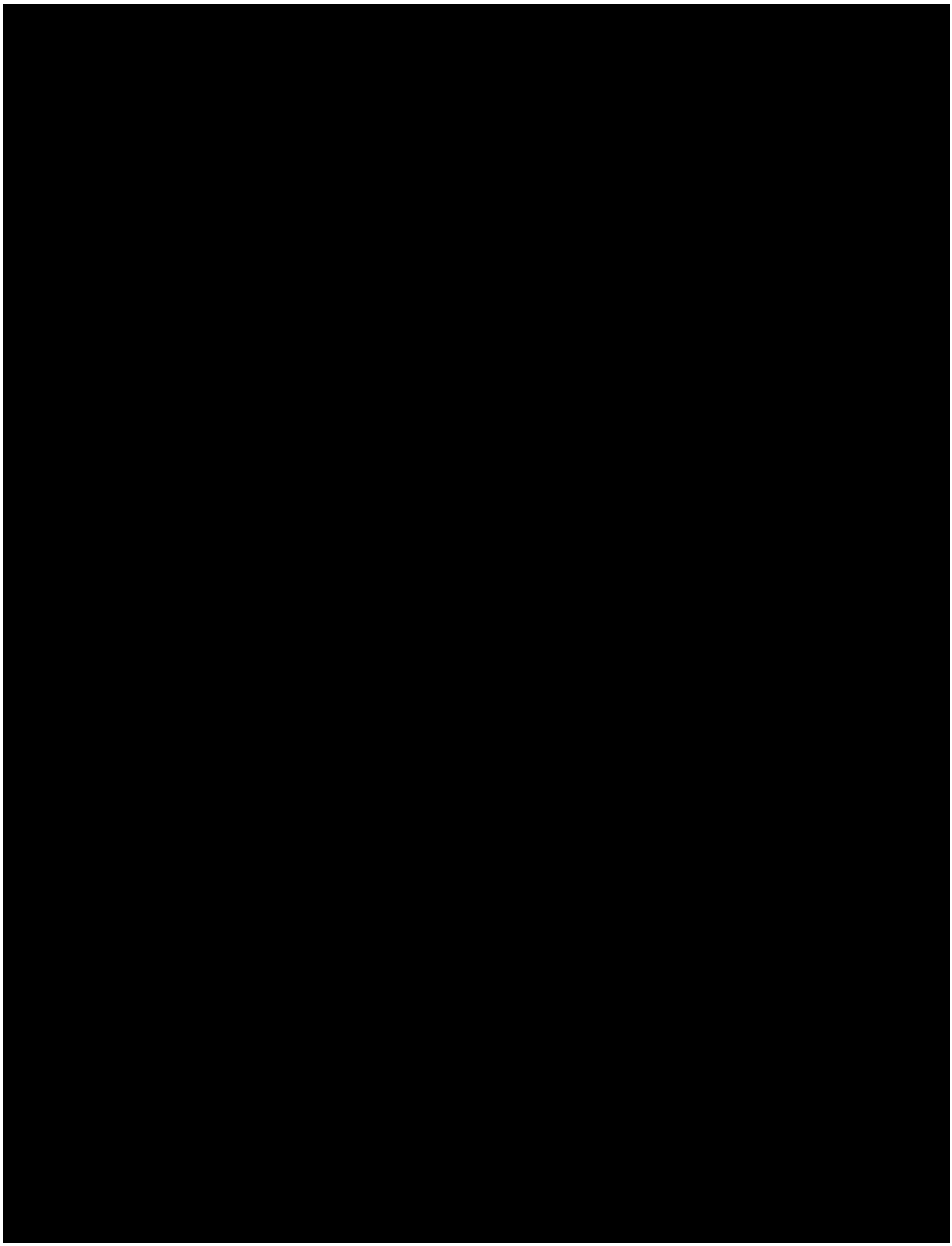
***Unscheduled PK and IG samples may be collected at any time if clinically indicated or at the Investigator's discretion. An unscheduled PK sample and IG sample should be collected upon confirmed disease progression.

8.5.2.2 Analytical method

Bioanalysis for pharmacokinetic studies will employ several validated assays:

- The assay to quantify MBG453 will be a validated liquid chromatography mass spectrometry (LC-MS) assay.
- Immunogenicity testing will consist a multi-tiered ADA testing. A screening assay will be used to assess clinical samples. Samples testing positive in the screening assay will then be subjected to a confirmatory assay to demonstrate that ADAs are specific for the therapeutic protein product. Samples identified as positive in the confirmatory assay will be further characterized in titration and neutralization assays.

[redacted]



[redacted]

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when both study treatments are stopped earlier than the protocol planned duration and can be initiated by either the subject or the investigator.

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

Study treatments must be discontinued under the following circumstances:

- Subject/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section (Section 6.2.2)
- Any situation in which study participation might result in a safety risk to the subject
- Following emergency unblinding
- Any adverse events or laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study
- Progression of disease (including transformation to acute leukemia per WHO 2016 classification, as defined as ≥20% blasts in bone marrow and/or peripheral blood), unless specific criteria to continue study treatment, in case there is no acute leukemia reported, as per Section 6.1.5.1, are met
- Termination of the study by Novartis
- Subjects who are scheduled for hematopoietic stem cell transplant (HSCT) or intensive chemotherapy at any time during the course of the study

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

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see 'Withdrawal of Informed Consent/Opposition to use data/biological samples' section). **Where possible, they should return for the assessments indicated for the End Of Treatment visit** 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 subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

[redacted]

Bone marrow aspirate/biopsy will be done as clinically indicated but every effort should be made to obtain a bone marrow sample at time of progression.

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

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

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

For details on AE/SAE reporting, please refer to Section 10.1.

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

The investigator must also contact the IRT to register the subject's discontinuation from MBG453 or placebo.

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code, Section 6.6.2.

All subjects who discontinued both study treatments will enter a long-term post-treatment and/or survival follow-up every 12 weeks after the end of treatment visit. Subjects who discontinued both study treatments due to reasons other than progression will have to perform hematology assessments every 12 weeks, and follow-up visits with PRO and response assessments as indicated in Table 8-1 until documented disease progression, death, lost to follow-up, withdrawal of consent/opposition to use data/biological samples. Survival and efficacy/PRO follow-up data will be collected for up to 5 years after the last subject was randomized.

In some circumstances, subjects may be allowed to continue to receive study treatment beyond disease progression as per criteria described at Section 6.1.5.1. These subjects will continue assessments as outlined in the assessments section (Section 8) and will complete the EOT visit only after permanent discontinuation of both study treatments.

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

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

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

and

- No longer wishes to receive study treatment

and

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

[redacted]

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

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

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

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

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

If the subject agrees, a final evaluation at the time of the subject's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table (refer to Section 8).

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

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw/oppose to the use of their data/biological samples, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. At least the information about the subject's survival status should be collected at the frequency described in Table 8-1. A subject should not be considered as lost to follow-up until due diligence has been completed (at least 3 failed documented attempts of contact), 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 subject welfare and safety. Should early termination be necessary, subjects must be seen or notified as soon as possible (before next scheduled study drug administration) and treated as a prematurely withdrawn subject. 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 subject'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.

[redacted]

9.1.5 Post treatment follow-up

Subjects who discontinue study treatment for reasons other than disease progression, death, lost to follow-up, or withdrawal of consent/opposition to use data/biological samples should continue the efficacy and PRO assessments as well as [redacted] as per Table 8-1 until progressive disease, withdrawal of consent/opposition to use data/biological samples, lost to follow-up, or death.

9.1.6 Survival follow-up

Subjects will be followed up for survival once study treatment is discontinued after disease progression, or once disease progression occurred in the post-treatment follow-up phase. Subjects will be contacted every 12 weeks to follow-up on their survival status and to complete PRO assessments. Any new anti-neoplastic therapies and transfusions that have been started since the previous contact will be collected. HSCT information will also be collected.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their End of Treatment or Follow-up visits and any repeat assessments associated with these visits have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

All treated subjects should have a safety follow-up for 30 days following the last dose of azacitidine and 150 days following the last dose of MBG453 or placebo. The safety follow-up can be done by telephone call or visit. The information collected is kept as source documentation. All AEs/SAEs reported during this time period must be reported as described in Section 10.1.1 and Section 10.1.3. Documentation of attempts to contact the subject should be recorded in the source documentation.

The OS futility analysis will be performed when approximately 72 OS events have occurred. The study may be terminated if the futility boundary is crossed following an assessment by the independent Data Monitoring Committee.

The OS primary analysis will be conducted when approximately 282 OS events have occurred. At this time, the primary clinical study report (CSR) will be produced. After the primary analysis, the study will remain open provided the OS demonstrates treatment benefit. Subjects still being followed on the study after the primary analysis time point will continue as per the schedule of assessments.

The end of study (Last patient last visit) is defined as the earliest occurrence of one of the following:

1. at the futility interim analysis if the study was stopped for lack of efficacy and all subjects discontinued study treatment,
2. at the primary analysis if the study failed to reject any null hypothesis and all subjects discontinued study treatment,
3. all subjects have died or discontinued from the study treatment and ended survival follow-up,
4. once all subjects were transitioned to treatment outside the study which is targeted at the latest 5 years after the last subject was randomized

[redacted]

At the end of the study, in alignment with local regulations, Post Trial Access (PTA) will be set up to provide MBG453 outside this study through an alternative setting to subjects who are receiving treatment with MBG453 and in the opinion of investigator are still deriving clinical benefit (see Section 6.1.5).

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 subject or clinical investigation subject 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 subject 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 subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

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

1. The Common Toxicity Criteria (CTC) AE grade (version 5.0). 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 subject
3. its duration (start and end dates or ongoing) and the outcome 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:

[redacted]

- Dose not changed
- Dose reduced/increased
- Drug interrupted/permanently discontinued

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.

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

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

Adverse event monitoring should be continued for at least

- 150 days after the last administration of MBG453/placebo, or 30 days after the last administration of azacitidine, whichever is later

OR

- until the start of a new post-treatment antineoplastic medication if sooner than the 150 days mentioned above. If a 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/placebo.

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

Disease progression (including fatal outcomes), if documented by use of appropriate method (for example, as per response assessment), should not be reported as a serious adverse event, please refer to Section 10.1.3 for more details.

Adverse events separate from the disease progression (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 [MBG453 Investigator's Brochure].

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

[redacted]

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 subjects 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 subject 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 subject'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 subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject 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.

[redacted]

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

10.1.3 SAE reporting

To ensure subject safety, SAEs occurring after the subject has provided informed consent and until 30 days after the date of the last actual administration of azacitidine or 150 days after the last dose of MBG453 or placebo must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). 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, unless otherwise specified by local law/regulations.

Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

The following SAE reporting timeframes apply:

- Screen Failures (e.g. a subject who is screened but is not treated or randomized): SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.
- Subjects receiving study treatment: SAEs must be collected between time subject signs ICF until 30 days after the subject has discontinued or stopped azacitidine, or 150 days after the subject has discontinued or stopped MBG453 or placebo.
- Subjects who were randomized but not treated with study treatment: SAEs must be collected between time subject signs ICF until discontinuation (no safety follow-up period required).

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, under no circumstances later than within 24 hours of the investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). 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), if documented by use of appropriate method (for example, as per response assessment), should be reported as a serious adverse event only 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 Package Insert (new occurrence) and is thought to be related to the study treatment, a Novartis Chief Medical Office and 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.

[redacted]

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

Pregnancies

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

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

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

Pregnancy data will not be collected from the female partners of any male subjects 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, subject or consumer (EMA definition).

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

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

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

[redacted]

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

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

For more information on AE and SAE definition and reporting requirements, please see the respective sections (Section 10.1.1 and Section 10.1.2).

10.2 Additional Safety Monitoring

10.2.1 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess safety data, critical efficacy variables and recommend to the sponsor whether to continue, modify, or terminate a trial.

Details regarding composition, responsibilities, data monitoring, meeting frequency, DMC reports, minutes and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

DMC Composition

It is expected that the DMC will consist at a minimum of two physicians with appropriate disease area qualifications and one statistician.

DMC Responsibilities

DMC will be responsible to review regularly safety data of subjects treated in the study.

It is envisioned that the DMC may make recommendations with regard to safety, namely:

- No safety issues, ethical to continue the study as planned
- Serious safety concerns precluding further study treatment
- Recommendation to continue the study but proposing an amendment to the protocol (e.g. incorporate an additional safety assessments)

If the study is recommended to continue by the DMC, no details about the safety results will be revealed.

DMC will also be responsible to review overall survival and relevant efficacy data of subjects randomized into the study at the time of the futility interim analysis and efficacy interim analysis.

It is envisioned that the DMC may make recommendations with regards to efficacy, namely:

- Recommendation to continue the study blinded as planned, no details about the efficacy results will be revealed

[redacted]

- Recommendation to continue the study blinded as planned but proposing to the Sponsor to unblind the interim results, if OS is statistically significant
- Recommendation to stop the study due to lack of efficacy, if OS cross the pre-specified futility boundary

DMC Meetings Frequency

The DMC will be established prior to the randomization of the first subject.

There will be an initial meeting with the DMC describing their roles and responsibilities and discussing potential data format and process prior to finalization of the DMC charter and the study analysis plan.

Thereafter, DMC will meet on a regular basis as described in the DMC Charter to review safety data from subjects receiving study drug. The frequency of the DMC safety reviews may vary and depends on the recruitment rate, the number of subjects on-treatment and upon DMC's request. They may also be notified periodically if concerns develop.

More specific details will be described in the DMC charter.

10.2.2 Steering Committee

The Steering Committee (SC) will be established comprising of investigators participating in the trial, i.e. not being members of the DMC and Novartis representatives from the Clinical Trial Team.

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.

[redacted]

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 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 subject 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.

Samples for some laboratory assessments, [redacted] and PK samples and/or data will be processed centrally and the results will be sent electronically to Novartis as described in the Data Transfer Specifications.

11.2 Database management and quality control

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

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

Dates of screenings, randomizations, screen failures, as well as randomization codes and data about investigational drug dispensed to the subject will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

At time of final analysis at study end, once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

[redacted]

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. 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 subject 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 subject 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 subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

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 subjects will be disclosed.

12 Data analysis and statistical methods

There will be two interim analyses for the primary endpoint OS, following a group sequential design:

- A futility interim analysis will be performed after approximately 72 OS events (40% information fraction of 180 events as per protocol version 00) have been documented.
- An efficacy interim analysis will be conducted when approximately 135 OS events (48% information fraction of 282 events as per protocol version 03) have been documented and when all subjects have been randomized.

In the absence of early stopping, a primary analysis will be performed after approximately 282 OS events have been documented. The final analysis will occur at the end of study.

All data will be summarized by treatment arm: baseline characteristics, efficacy data for the Full Analysis Set, safety and other data (unless specified otherwise) for the Safety Set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum as well as 25^{th} and 75^{th} percentiles will be presented.

[redacted]

12.1 Analysis sets

Full Analysis Set: FAS

The Full Analysis Set (FAS) comprises all subjects to whom study treatment has been assigned by randomization. According to the intent to treat principle, subjects will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure.

Safety Set

The Safety Set includes all subjects who received at least one dose of any component of the study treatment (MBG453+azacitidine or placebo+azacitidine). Subjects will be analyzed according to the treatment they received, either MBG453+azacitidine or placebo+azacitidine. If the subjects never received the investigational drug (i.e. MBG453 or placebo) and took at least one dose of azacitidine, subjects will be analyzed in the placebo+azacitidine arm.

Pharmacokinetic Analysis Set: PAS

The Pharmacokinetic Analysis Set (PAS) includes all subjects in the Safety Set, who had at least one evaluable PK concentration.

For a concentration to be evaluable:

- Dosing information must be properly documented (data and time of administration)
- For pre-dose samples: the sample is collected before the next dose administration
- For post-dose samples: planned dose of MBG453 must be taken prior to sampling

12.2 Subject 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

The duration of exposure will be summarized for study treatment and for each study drug (MBG453, placebo and azacitidine). 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 subjects with dose adjustments (reductions for azacitidine 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.

[redacted]

12.4 Analysis of the primary endpoint(s)

12.4.1 Definition of primary endpoint(s)

The primary endpoint is Overall Survival defined as time from randomization until death due to any cause, regardless of start of new therapies, HSCT, or discontinuation of treatment. If a subject is not known to have died, then OS will be censored at the latest date the subject was known to be alive (on or before the cut-off date).

The primary estimand is described by the following four attributes:

- A. The **population** is defined as higher-risk MDS/CMML-2 subjects as defined by selection criteria.
- B. The primary **variable** is OS.
- C. The **treatment** is the intended study treatment of azacitidine+MBG/placebo, followed by any standard of care therapy including HSCT and new antineoplastic therapies.
- D. **Intercurrent events** may affect the interpretation of the variable. Based on the treatment attribute definition, OS will be analyzed regardless of treatment discontinuation, start of further anti-neoplastic therapy or HSCT.
- E. The **summary measure** is the hazard ratio (HR) for OS between two treatment arms. It will be estimated using Cox proportional hazard model stratified by randomization stratification factors. The primary comparison will be performed using log-rank test stratified by randomization stratification factors.

12.4.2 Statistical model, hypothesis, and method of analysis

Assuming proportional hazards model for OS, the following statistical hypotheses will be tested to address the primary efficacy objective for OS:

$H_{01} : \theta 1 \geq 1$ vs. $H_{a1} : \theta 1 < 1$

where $\theta 1$ is the OS hazard ratio (MBG453+azacitidine versus placebo+azacitidine).

The analysis to test these hypotheses and compare the two treatment groups will consist of a stratified log-rank test at an overall one-sided 2.5% level of significance. The stratification will be based on the randomization stratification factors in 4 groups: i.e. Intermediate risk MDS, High risk MDS, Very high risk MDS, CMML-2.

OS analysis will be made as a part of a three-look group sequential design using a Lan-DeMets (O'Brien-Fleming) alpha spending function.

Analyses will be based on the Full analysis set according to the randomized treatment group and strata assigned at randomization. The OS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, quartiles and associated 95% confidence intervals will be presented for each treatment group. The hazard ratio for OS will be calculated, along with its 95% confidence interval, from a stratified Cox model using the same randomization stratification factors as for the log-rank test.

[redacted]

12.4.3 Handling of missing values/censoring/discontinuations

OS will be censored at the date of the last contact date if a subject is not known to have died at or prior to the analysis cut-off date. All deaths at or prior to cut-off date will be taken into account whenever the death occurred, i.e. even after new anti-neoplastic therapy, SCT, interruptions, or discontinuation of study treatment due to any reason.

12.4.4 Supportive analyses

Subgroup analyses for OS

If the primary endpoint analyses for OS are statistically significant at the efficacy IA or primary analysis, subgroup analyses to assess the homogeneity of the treatment effect will be performed for the subgroups as shown below:

- Intermediate risk MDS, High risk MDS, Very high risk MDS, CMML-2 as per randomization.

Additional subgroup analyses may be conducted for OS. Details will be specified in the SAP.

The number of subjects censored and reasons for OS censoring will be summarized by treatment arm.

12.5 Analysis of secondary endpoints

12.5.1 Key secondary objectives

The first two key secondary objectives of the study are to compare time to definitive deterioration (TTDD) of fatigue and RBC transfusion-free intervals (TFI) between the two treatment arms. Additional three key secondary objectives will be tested in a hierarchical approach described in Section 12.5.1.3.

The type I error control for this key secondary endpoint family is described in Section 12.5.1.4.

12.5.1.1 Time to definitive deterioration (TTDD) of fatigue

Time to definitive deterioration (TTDD) of fatigue is defined as time from randomization to

- at least 3 points worsening from baseline in FACIT-fatigue scores with no subsequently observed improvement above this threshold, or
- death due to any cause,

whichever occurs first. Subjects without TTDD event will have their TTDD censored at the time of the last adequate assessment performed on or before cut-off date.

A threshold of at least 3 points worsening from baseline in the FACIT fatigue score is based on Cella et al 2002.

The primary estimand is described by the following attributes:

- A. The **population** is defined as higher-risk MDS/CMML-2 subjects as defined by selection criteria.
- B. The primary **variable** is TTDD.

[redacted]

- C. The **treatment** is the intended study treatment of azacitidine+MBG/placebo, followed by any standard of care therapy including HSCT and new antineoplastic therapies.
- D. **Intercurrent events**: Based on the treatment attribute definition, TTDD will be analyzed regardless of treatment discontinuation, start of further anti-neoplastic therapy or HSCT.
- E. The **summary measure** is the hazard ratio (HR) for TTDD between two treatment arms. It will be estimated using Cox proportional hazard model stratified by randomization stratification factors. The primary comparison will be performed using log-rank test stratified by randomization stratification factors.

For subjects without TTDD event, TTDD is censored at last adequate assessment. This is the last FACIT-Fatigue assessment conducted that is not missing.

For TTDD, a death event occurring after two or more consecutive missing assessments (not done or unknown) is censored in the analysis at the last adequate FACIT-Fatigue assessment before the event date and reason for censoring then summarized as 'Death documented after two or more missing assessments'.

For those subjects who cannot deteriorate (i.e. patients with a baseline score < 3), TTDD will be censored at randomization date unless deteriorate due to death (i.e. if death occurring after two or more consecutive missing assessments, then TTDD will be censored at the randomization date).

Assuming proportional hazards model for TTDD of fatigue, the following statistical hypotheses will be tested at the 1-sided alpha-TTDD level of significance:

H_{02} (null hypothesis): $\theta 2 \geq 1$ vs H_{a2} (alternative hypothesis): $\theta 2 < 1$

where θ2 is the TTDD hazard ratio (MBG453+azacitidine versus placebo+azacitidine).

The analysis to test this hypothesis will consist of a stratified log-rank test at the alpha-TTDD level of significance (see Section 12.5.1.4 for definitions). The same randomization stratification factors as for the OS analysis will be used.

12.5.1.2 RBC transfusion-free intervals (TFI)

RBC transfusion-free intervals (TFI) correspond to cumulative times of intervals with no evidence of RBC transfusion for at least 8 weeks at any point after randomization until death due to any cause.

Only RBC transfusions due to MDS or CMML-2 will be considered for this analysis. If the RBC transfusion-free interval is terminated by the resumption of RBC transfusion, the subjects remains "at risk", i.e. for such a subject, there can be another RBC transfusion-free interval later in time. As per the definition above, this analysis will label days where no transfusion was given as "transfusion-free" only if they fall into a transfusion-free interval lasting at least 8 weeks.

The primary outcome is the annualized RBC transfusion-free rate (TFR), which is defined as the average number of days in RBC transfusion-free intervals in a year (i.e., the total number of days in RBC transfusion-free intervals divided by the total days in the study multiplied by 365.25). The annualized RBC transfusion-free rate is estimated in a negative binomial (NB) model by using the number of days in RBC transfusion-free intervals as the response variable with natural log of time in study as an offset variable.

[redacted]

Under the Negative binomial (NB) model, the following statistical hypotheses will be tested at the 1-sided alpha-TF level of significance:

- H_{03} (null hypothesis): $\mu_{MBG453+azacitidine} \leq \mu_{placebo+azacitidine}$
- H_{a3} (alternative hypothesis): $\mu_{MBG453+azacitidine} > \mu_{placebo+azacitidine}$

where $\mu_{MBG453+azacitidine}$ and $\mu_{placebo+azacitidine}$ are the annualized RBC transfusion-free rates under the two treatments, respectively.

The hypotheses will be tested using a negative binomial regression model with log link, using treatment as covariates. Randomization stratification factors and baseline transfusion status (see Table 8-2) will be used as stratification factors in this analysis.

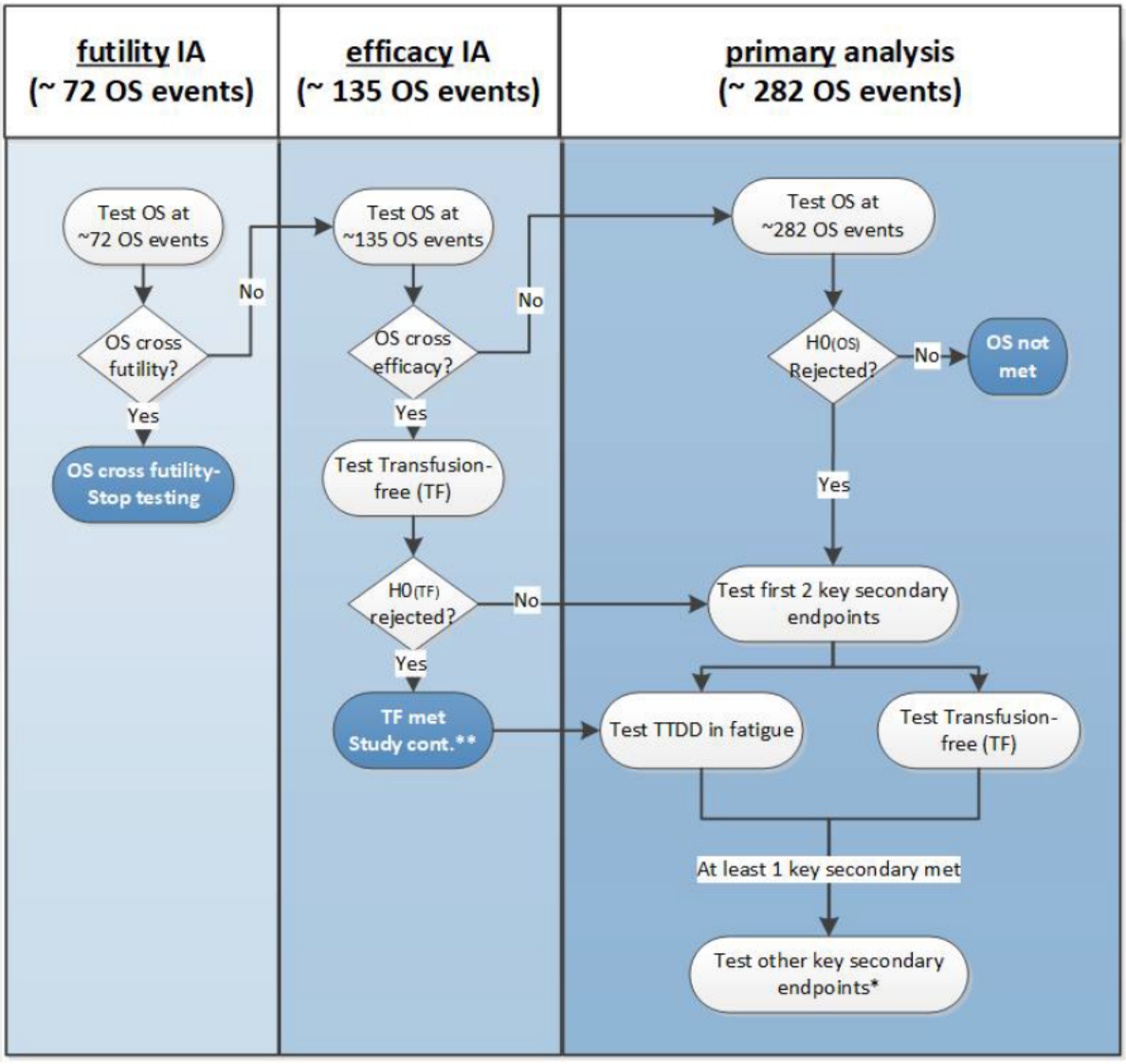
12.5.1.3 Hypothesis testing strategy

If OS is statistically significant at the efficacy interim or at the primary analysis, the key secondary endpoints will be tested according to the testing strategy as described in Figure 12-1:

- Time to definitive deterioration (TTDD) of fatigue
- RBC transfusion-free intervals
- Fatigue improvement rate
- Physical functioning improvement rate
- Emotional functioning improvement rate

[redacted]

Figure 12-1 Study flow of analyses and testing strategy



*If at least one of the two first key secondary endpoint is statistically significant, the following key secondary endpoints will be tested in a sequence, considering hierarchical testing scheme: (1) FACIT fatigue improvement rate (2) EORTC physical function improvement rate (3) EORTC emotional function improvement rate

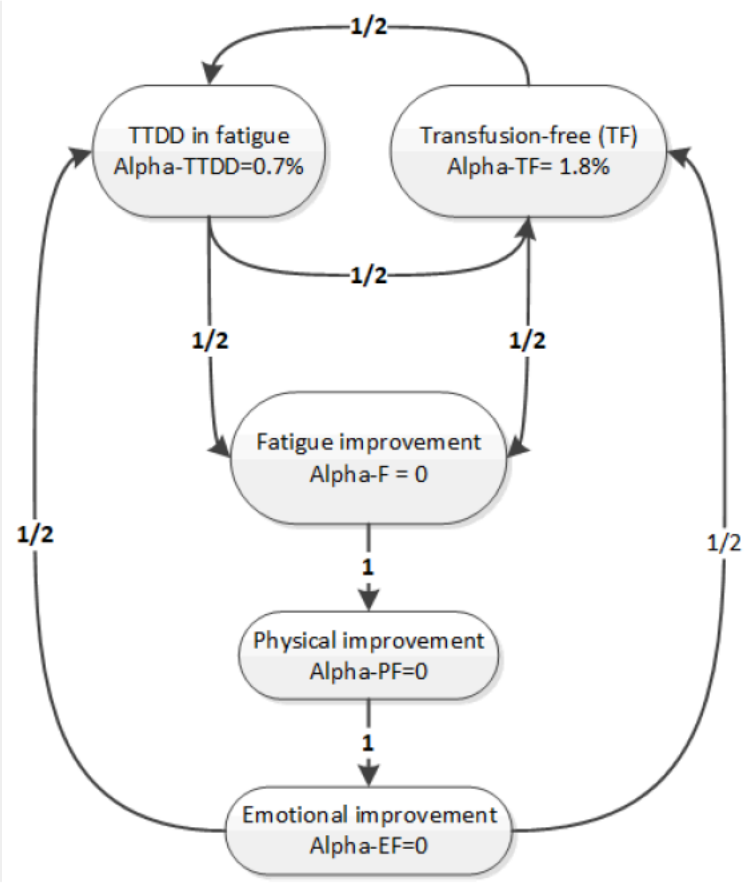
**If transfusion-free (TF) is statistically significant at the efficacy IA, then it will not be tested again at the primary analysis. The initial alpha-TF-IA assigned will be transferred to other endpoints following the gate-keeping procedure in Figure 12-2.

[redacted]

12.5.1.4 Gate-keeping procedure

In order to conserve the overall type I error (1-sided level of significance α = 2.5%) in this testing strategy, an alpha split with a graphical gate-keeping approach will be implemented as shown in Figure 12-2 below based on the graphical multiple testing procedure by Bretz et al 2009, Bretz et al 2011.

Figure 12-2 Graphical gate-keeping procedure in order to control overall type I error



The alpha-TTDD of 0.7% and the alpha-TF of 1.8% are the starting values of the graphical testing procedure. The alpha-TF is the overall alpha assigned to TF, which is further split into 0.2% for the efficacy interim and 1.6% for the primary analysis.

This graphical gate-keeping procedure with the above mentioned initial alpha split and propagation ensures the protection of an overall one-sided type-I error of α = 2.5%. With exception of TF, all the other endpoints in this scheme will only be tested at the corresponding alpha's at the primary analysis.

For TF, the overall assigned alpha-TF will be split between the efficacy IA and primary analysis, with the starting value of alpha level of 0.2% at the efficacy IA and alpha level of 1.6% at the primary analysis. If TF receives alpha, it will always go entirely to the alpha level at the primary analysis. A fixed alpha-level of 0.00001 will be spent for TTDD at the time of the efficacy interim analysis.

[redacted]

For example, at the efficacy interim analysis, if RBC transfusion-free intervals is statistically significant, it will not be tested again at the primary analysis. The overall alpha-TF of 1.8% will be transferred to TTDD and Fatigue improvement rate equally. Thus, at the primary analysis, TTDD will be tested at an updated starting value of alpha-TTDD 1-sided level of significance of 0.7%+0.9% = 1.6%; and fatigue improvement rate will be tested at an updated starting value of alpha-F 1-sided level of significance of 0.9 %.

12.5.1.5 PRO improvement rates

FACIT Fatigue improvement rate

For FACIT-Fatigue scale score, the responder is defined as having 3 points improvement from baseline confirmed by a second improvement of 3 points, regardless of preceding worsening. A subject who cannot improve will be considered as a non-responder.

The primary estimand is described by the following attributes:

- A. The **population** is defined as higher-risk MDS/CMML-2 subjects as defined by selection criteria.
- B. The primary **variable** is the proportion of subjects having 3 points improvement from baseline confirmed by a second improvement of 3 points.
- C. The **treatment** is the intended study treatment of azacitidine+MBG/placebo, followed by any standard of care therapy including HSCT and new antineoplastic therapies.
- D. **Intercurrent events**: Based on the treatment attribute definition, the improvement rate will be analyzed regardless of treatment discontinuation, disease progression, start of further anti-neoplastic therapy or HSCT.
- E. The **summary measure** is the proportion of responders between two treatment arms. It will be estimated using Cochran-Mantel-Haenszel method stratified by randomization stratification factors.

The following statistically hypothesis will be tested at the alpha-F level of significance:

- H_{04} (null hypothesis): $F_{MBG453+azacitidine} \leq F_{placebo+azacitidine}$
- H_{a4} (alternate hypothesis): $F_{MBG453+azacitidine} > F_{placebo+azacitidine}$

where $F_{MBG453+azacitidine}$ and $F_{placebo+azacitidine}$ are the probabilities of fatigue responders on MBG453+azacitidine and placebo+azacitidine arms.

The proportion of responders and its 95% confidence interval (CI) will be summarized by treatment arms. Stratified Cochran-Mantel-Haenszel method controlling for randomization stratification factors will be used to evaluate the treatment effect on the proportions of responders between treatment arms. Odds ratios with 2-sided 95% confidence interval, by randomization stratification factor and overall, will be presented. Exact method will be considered if the numbers of responders in most of the strata are low.

[redacted]

[redacted]

EORTC - Physical functioning improvement rate

For EORTC physical functioning scale, the responder is defined as having 10 points improvement from baseline confirmed by a second improvement of 10 points, regardless of preceding worsening. A subject who cannot improve will be considered as a non-responder.

The primary estimand is described by the following attributes:

- A. The **population** is defined as higher-risk MDS/CMML-2 subjects as defined by selection criteria.
- B. The primary **variable** is the proportion of subjects having 10 points improvement from baseline confirmed by a second improvement of 10 points.
- C. The **treatment** is the intended study treatment of azacitidine+MBG/placebo, followed by any standard of care therapy including HSCT and new antineoplastic therapies.
- D. **Intercurrent events**: Based on the treatment attribute definition, the improvement rate will be analyzed regardless of treatment discontinuation, disease progression, start of further anti-neoplastic therapy or HSCT.
- E. The **summary measure** is the proportion of responders between two treatment arms. It will be estimated using Cochran-Mantel-Haenszel method stratified by randomization stratification factors.

The following statistically hypothesis will be tested at the alpha-PF level of significance:

- H_{05} (null hypothesis): $PF_{MBG453+azacitidine} \leq PF_{placebo+azacitidine}$
- H_{a5} (alternate hypothesis): $PF_{MBG453+azacitidine} > PF_{placebo+azacitidine}$

where $PF_{MBG453+azacitidine}$ and $PF_{placebo+azacitidine}$ are the probabilities of physical functioning responders on MBG453+azacitidine and placebo+azacitidine arms.

The proportion of responders and its 95% CI will be summarized by treatment arms. Stratified Cochran-Mantel-Haenszel method controlling for randomization stratification factors will be used to evaluate the treatment effect on the proportions of responders between treatment arms. Odds ratios with 2-sided 95% confidence interval, by randomization stratification factor and overall, will be presented. Exact method will be considered if the numbers of responders in most of the strata are low.

[redacted]

EORTC - Emotional functioning improvement rate

For EORTC emotional functioning scale, the responder is defined as having 10 points improvement from baseline confirmed by a second improvement of 10 points, regardless of preceding worsening. A subject who cannot improve will be considered as a non-responder.

The primary estimand is described by the following attributes:

- A. The **population** is defined as higher-risk MDS/CMML-2 subjects as defined by selection criteria.
- B. The primary **variable** is the proportion of subjects having 10 points improvement from baseline confirmed by a second improvement of 10 points.

[redacted]

- C. The **treatment** is the intended study treatment of azacitidine+MBG/placebo, followed by any standard of care therapy including HSCT and new antineoplastic therapies.
- D. **Intercurrent events:** Based on the treatment attribute definition, the improvement rate will be analyzed regardless of treatment discontinuation, disease progression, start of further anti-neoplastic therapy or HSCT.
- E. The **summary measure** is the proportion of responders between two treatment arms. It will be estimated using Cochran-Mantel-Haenszel method stratified by randomization stratification factors.

The following statistically hypothesis will be tested at the alpha-EF level of significance:

- H_{06} (null hypothesis): $EF_{MBG453+azacitidine} \leq EF_{placebo+azacitidine}$
- H_{a6} (alternate hypothesis): $EF_{MBG453+azacitidine} > EF_{placebo+azacitidine}$

where $EF_{MBG453+azacitidine}$ and $EF_{placebo+azacitidine}$ are the probabilities of emotional functioning responders on MBG453+azacitidine and placebo+azacitidine arms.

The proportion of responders and its 95% CI will be summarized by treatment arms. Stratified Cochran-Mantel-Haenszel method controlling for randomization stratification factors will be used to evaluate the treatment effect on the proportions of responders between treatment arms. Odds ratios with 2-sided 95% confidence interval, by randomization stratification factor and overall, will be presented. Exact method will be considered if the numbers of responders in most of the strata are low.

[redacted]

12.5.2 Efficacy and/or Pharmacodynamic endpoint(s)

Progression Free Survival

PFS is defined as the time from the date of randomization to the date of the first documented progression/relapse from CR per investigator assessment or death due to any cause. Progression includes transformation to acute leukemia as per WHO 2016 classification. A subject without PFS event will have their PFS censored at the time of the last adequate response assessment performed on or before the cut-off date.

Leukemia-free Survival

Leukemia-free survival is defined as the time from date of randomization to ≥ 20% blasts in bone-marrow/peripheral blood as per WHO 2016 classification, appearance of chloroma, or death due to any cause. For subject without event, the time is censored at the latest date the subject was known to be alive and without leukemia (on or before the cut-off date).

Response Rate

Response rate is defined as the proportion of subjects with best overall response of either complete remission (CR)/marrow remission (mCR)/partial remission (PR)/hematologic improvement (HI) at any time during the study (on or before cut-off date) as per investigator assessment (for definitions, see Table 8-2). Response rates will be provided with exact 95%

[redacted]

confidence intervals (Clopper CJ and Pearson 1934). Subgroup analyses of response rate by blasts percentage at baseline (≤ 5% or > 5%) will be performed.

In order to be classified as CR, no progression or relapse from CR should be reported within the following 4 weeks.

Stable Disease (SD) rate is defined as the proportion of subjects with best overall response of SD per investigator assessment at any time during the study (on or before cut-off date). Any hematologic improvement with exact 95% confidence intervals will be reported separately.

Improvement in Transfusion Independence

RBC/Platelets transfusion independence rate is defined as the proportion of subjects having received 0 units of RBC/Platelets transfusions during at least 8 consecutive weeks after randomization. The number and percentage of subjects will be shown for the overall FAS and then also in only those with transfusion dependence at baseline (for definitions, see Table 8-2). Percentages will be provided with exact 95% confidence intervals (Clopper CJ and Pearson 1934).

12.5.3 Safety endpoints

For all safety analyses, the safety set will be used.

On-treatment period for safety analyses

For safety reporting, the overall observation period will be divided into three mutually exclusive segments:

- **Pre-treatment period**: from day of subject's informed consent to the day before first dose of study treatment
- **On-treatment period**: from day of first dose of study medication to 30 days after date of last administration of study treatment (MBG453, placebo or azacitidine)
- **Post-treatment period**: starting at day 30+1 after date of last administration of study treatment (MBG453, placebo or azacitidine).

Overall safety period: from date of first administration of study treatment to 30 days after the date of the last administration of azacitidine or 150 days after the last dose of MBG453 or placebo, whichever is later.

Adverse events

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

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

[redacted]

The number (and percentage) of subjects with adverse events will be summarized by treatment arm, 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.

In addition, 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 period and overall safety period will be flagged.

Vital signs

All vital signs abnormalities will be summarized by treatment arm.

Clinical laboratory evaluations

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

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

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

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

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

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

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

Other safety evaluations

ECOG

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

12.5.4 Pharmacokinetics

When feasible, the pharmacokinetic parameters in Table 12-1 will be determined by profiles using noncompartmental method(s) for MBG453 in Chinese patients in PK subgroup.

[redacted]

Table 12-1 Noncompartmental pharmacokinetic parameters

Parameter	Definition
AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1)
AUCinf	The AUC from time zero to infinity (mass x time x volume-1)
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1)
Cmax	The maximum (peak) observed drug concentration after single dose administration (mass x volume-1)
Tmax	The time to reach maximum (peak) drug concentration after single dose administration (time)
T1/2	The terminal half-life associated with the terminal slope ((λz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives
CL	The total body clearance of drug from the blood circulation (volume x time-1)
Vz	The apparent volume of distribution during terminal phase (associated with (λz) (volume)

PAS will be used in all pharmacokinetic data analyses. Descriptive statistics of all pharmacokinetic parameters, including arithmetic and geometric mean, median, SD, and CV, geometric CV, minimum and maximum, will be presented by cycle. Descriptive statistics (n, m (number of non-zero concentrations), mean, coefficient of variation (CV%), standard deviation, median, geometric mean, geometric CV%, minimum and maximum) for MBG453 concentration will be presented at each scheduled timepoint. Below the limit of quantitation (BLQ) values will be set to zero by the Bioanalyst and will be displayed in the listings as zero and flagged. However, BLQ values will be treated as missing for the calculation of the geometric means and geometric CV%. Missing values for any PK parameters or concentrations will not be imputed and will be treated as missing.

All concentration data for MBG453 vs. time profiles will be displayed graphically.

MBG453 serum concentration data will be listed by treatment, subject, and visit/sampling time point. The concentrations collected before dose administration on Day 8 of Cycle 3 and beyond are Ctrough for MBG453.

Population pharmacokinetic analysis

If data permit, a mixed-effects model may be applied to the serum MBG453 concentration-time data from this study along with other studies to generate post-hoc estimates of pharmacokinetic parameters using appropriate software to characterize MBG453 exposure and to determine the effects of intrinsic (i.e. demographic factors) and extrinsic covariates (e.g. combination partners) on MBG453 exposure. If there is sufficient data for analysis, the details of the population pharmacokinetic analyses may be provided in a separate reporting and analysis plan, and the results may be reported in a separate population pharmacokinetic report.

12.5.4.1 Immunogenicity

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

[redacted]

12.5.5 Patient reported outcomes

To assess the Global health and overall QoL:

Change from baseline in EQ-5D-5L, VAS over time will be summarized using descriptive statistics, at each scheduled assessment timepoint for each treatment arm.

Change from baseline to Cycle 12 Day 1 in Global health status using EORTC will be summarized using descriptive statistics for each treatment arm.

Change from baseline in FACIT-fatigue, EORTC-physical function, EORTC-emotional function over time until death will be summarized using descriptive statistics, at each scheduled assessment timepoint for each treatment arm.

All assessments will be taken into account whatever these assessments occurred after/before responses/progression, new antineoplastic therapy, concomitant treatment (including transfusion), SCT, interruptions or discontinuation of study treatment due to any reason.

[redacted]

[redacted]

[redacted]

12.7 Interim analyses

The primary efficacy analyses on overall survival will be based on the full analysis set and are event driven.

- primary analysis will be performed when approximately 282 OS events have been documented.
- futility interim analysis (IA) will be performed when approximately 40% of 180 OS events as per protocol version 00 have occurred.
- efficacy IA will be performed when approximately 48% of 282 OS events have occurred and all subjects have been randomized.

Futility IA

The futility IA will be performed when there are approximately 72 OS events. Probability of Success (PoS) will be used to determine futility boundary at the futility IA. Details are specified in the statistical appendix.

At the time of the futility IA, the OS data available from the parallel ongoing Phase II study [CMBG453B12201] will be used to construct a prior to calculate the probability of success (PoS). PoS is defined as the marginal conditional probability of achieving statistical significance of the primary OS endpoint at either the efficacy interim or the primary analysis, given the Phase II and Phase III data available at the time of the Phase III futility interim. It is calculated by averaging the conditional Phase III power function over the posterior distribution for the log hazard ratio given the available Phase II and Phase III OS data. The study will be terminated for lack of efficacy after the futility IA if the PoS is less than 15%.

- If the futility IA occurs before CR rate analysis of [CMBG453B12201] study, no phase II study data will be used.
- If the futility IA occurs after CR rate analysis and before the PFS IA of [CMBG453B12201] study, OS data collected until CR rate analysis in Phase II will be used.
- If the futility IA occurs after PFS IA of [CMBG453B12201] study, OS data collected until PFS IA in Phase II will be used.

Efficacy IA

The efficacy IA will be performed when there are approximately 135 OS events and when all subjects have been randomized. Group sequential plan using Lan and DeMets α-spending approach with O'Brien-Fleming type boundary (Lan and DeMets 1983) as implemented in the software East 6.4 will be applied. The study will conclude for efficacy at the efficacy IA if the null hypothesis is rejected at one-sided significance 0.0012 (corresponding hazard ratio (HR) threshold assuming proportional hazards: HR < 0.593).

[redacted]

If OS is significant at the efficacy interim, it will not be tested again at the primary analysis, but the OS analysis will be updated at the primary analysis.

No external data will be used for the efficacy IA and primary analysis.

Primary Analysis

The primary analysis will be performed when there are approximately 282 OS events. The projected timing of interim and primary analysis is summarized in Table 12-2.

A simulation in East 6.4 of 10000 trials of the described setup of protocol version 03 (simulating for each trial the individual outcomes for the fully recruited 530 patients, using actual recruitment distribution and following group-sequential design with an interim at 135 events) was conducted and the percentage of significant trial analysis results recorded. A piecewise exponential model was used which assumed a constant hazard rate of 0.035 in both treatment arms in the first 5 months after treatment start (piece 1) and 0.021 and 0.035, respectively, (HR=0.6) subsequently (piece 2). Based on total 282 OS events at primary analysis, the cumulative probability to detect an efficacious treatment by the primary analysis is 85%, while the cumulative probability of erroneously detecting a non-efficacious treatment by the primary analysis is 2.4%.

Since the futility analysis was already conducted under protocol version 00 (40% information fraction out of the planned 180 events per protocol version 00), no changes were made to the thresholds for declaring futility or their calculation. If the primary null hypothesis as per protocol version 00 was true, then the probability to stop the trial at the futility analysis was 73%.

The futility and efficacy interim analyses for OS will be performed by an independent statistician. Results from OS interim analyses will not be communicated to clinical team or any party involved in the study conduct (apart from the independent statistician and IDMC members) or external parties including Health Authority and investigators, until OS is found to be significant or study needs to be terminated due to safety or lack of efficacy.

[redacted]

Table 12-2 Estimated timelines for interim and primary analysis assuming 5 months delayed effects

Months after randomization of the first subject (approximation)	Intent of Analysis	# OS events (Information Fraction)	Decision threshold (PoS for futility or alpha-threshold and corresponding HR for efficacy)	Boundary Crossing Probability
17	IA for Futility	72 (40% of 180 events as per protocol version 00)	15%	73%[b]
22[e]	IA for Efficacy	135 (48% of 282 events as per protocol version 03)[a]	α<0.0012 (HR <0.593)[d]	3%[c]
44[e]	primary	282 (100% of 282 events as per protocol version 03)[a]	α<0.0246 (HR <0.791)[d]	85%[c]

[a] Efficacy interim and primary analysis using O'Brien-Fleming boundaries in Group Sequential Design

[b] The futility boundary crossing probability was calculated under null hypothesis in Phase III and under null hypothesis in Phase II, based on the assumption that OS data from CR analysis of [CMBG453B12201] was available at the time of futility interim analysis

[c] The efficacy boundary crossing probability is calculated under alternative hypothesis (HR=1 for the first 5 months followed by HR=0.6) using East 6.4

[d] Alpha-thresholds and corresponding HR thresholds (assuming proportional hazards) are calculated using East 6.4

[e] timeline estimated based on actual recruitment distribution

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The sample size calculation is based on the primary variable OS. The hypotheses to be tested and details of the testing strategy are described in Section 12.4.2.

With 282 OS events and assuming a delayed onset of effect of 5 months followed by HR=0.6, the cumulative probability to detect an efficacious treatment by the primary analysis is 85% based on 10000 simulations in East 6.4 using the piecewise exponential model described in Section 12.7. The median OS for Placebo+HMA is assumed to be 20 months and actual recruitment pattern at time of protocol version 03 was used.

This calculation assumes analysis by a one-sided log-rank test at the overall 2.5% level of significance where subjects are randomized to the two treatments in a 1:1 ratio. Assuming that total enrollment time will be 20 months (based on the observed recruitment rate), and losses to follow-up of 10% per treatment arm per year, a total of 500 subjects will need to be randomized to observe the targeted 282 OS events at about 44 months after the randomization date of the first subject. These calculations were made using the software package East 6.4 and R 3.4.3.

[redacted]

The efficacy analyses on overall survival will be based on full analysis set and are event driven. Primary analysis will be performed when there are approximately 282 OS events. A futility interim analysis will be performed when approximately 40% of the 180 OS events as per protocol version 00 have occurred. A efficacy interim analysis will be performed when approximately 48% of the 282 OS events have occurred and all subjects have been randomized.

12.8.2 Secondary endpoint(s)

The hypotheses to be tested and details of the testing strategy for the two key secondary endpoints are provided in Section 12.5.1.

Time to definitive deterioration (TTDD) of fatigue

Based on available data from previous study [CETB115D2301], out of the subjects remaining on study, the median of FACIT fatigue showed a worsening of 3 point from baseline by Cycle 14. Taking into account that the Kaplan-Meier first quartile estimate of OS in the azacitidine+placebo was 273 days (about 9 months), we assume the median TTDD of fatigue as 9 months for azacitidine+placebo arm in this study. It is hypothesized that treatment with MBG453+ azacitidine will result in a 40% reduction in the hazard ratio for TTDD, i.e. an expected hazard ratio of 0.6 which corresponds to a median TTDD of fatigue of 15 months in MBG453+ azacitidine arm under the exponential model assumption.

If OS is significant at the primary analysis, and assuming an HR of 0.6 for TTDD, it is calculated that approximately 180 TTDD events are observed which ensures 90% power at the primary analysis with an alpha-TTDD level of 1.6%.

RBC Transfusion-free intervals

Based on available data from previous study [CETB115D2301], out of 164 subjects randomized in azacitidine+placebo arm, from Cycle 1 to Cycle 4, 123 (75%) subjects needed RBC transfusions, with a median of 5 RBC transfusions and standard deviation of 5.06.

We assume the over-dispersion parameter (k=0.5) and the annualized RBC transfusion-free rate for subjects treated with azacitidine+placebo is $\mu_{placebo+azacitidine} = 0.25$, the annualized RBC transfusion-free rate for those treated with MBG453+ azacitidine is $\mu_{MBG453+azacitidine} = 0.385$. Therefore, the estimated annualized transfusion-free rate increase for MBG453+azacitidine versus azacitidine+placebo is 35%. A total number of 500 subjects will give overall 91% statistical power at a 1-sided significance level of 0.016 given OS is significant.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

[redacted]

13.2 Responsibilities of the investigator and IRB/IEC

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

13.3 Publication of study protocol and results

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

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

13.4 Quality Control and Quality Assurance

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

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

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

14 Protocol adherence

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

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

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

14.1 Protocol amendments

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

Only amendments that are required for subject 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 subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

[redacted]

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[redacted]

16 Appendices

16.1 Appendix 1: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-1 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 m²**	• 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

[redacted]

Table 16-2 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

16.2 Appendix 2: Guidance to support eligibility evaluation based on serologic markers for hepatitis B

Please consider the general guidelines below, investigators may consult specialists to decide subjects eligibility in case of borderline results

Protocol exclusion criterion:

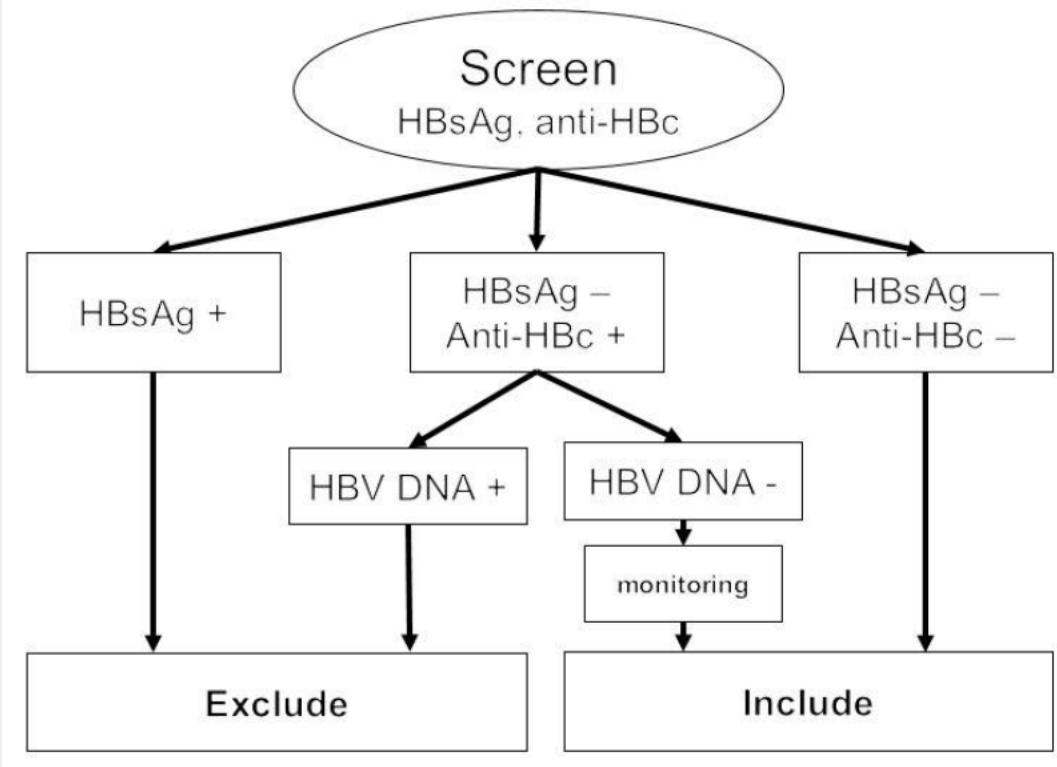
- Positive serology for hepatitis B surface antigen (HBsAg)
- Positive serology for hepatitis B core antibody (HBcAb), except if both criteria are met:
  1. HBV DNA negative
  2. Hepatitis HBV monitoring is implemented: HBsAg or HBV DNA should be tested every 6 weeks for the first 6 months and every 12 weeks thereafter, until the end of study. Upon consultation with a specialist, if the management plan proposed differs from this, Novartis global team should be consulted.

Table 16-3 Eligibility based on serologic markers for hepatitis B

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

[redacted]

Figure 16-1 Decision tree to determine eligibility based on serologic markers for hepatitis B



16.3 Appendix 3: Statistical details of leveraging phase II study CMBG453B12201 data in the futility interim analysis

This appendix provides details of the statistical models, the futility interim analysis decisions for hypothetical data scenarios and the operating characteristics.

The futility interim analysis was performed before the release of protocol version 03, therefore this appendix has not been updated.

16.3.1 Background

The primary efficacy analyses on overall survival will be based on the full analysis set and are event driven. The futility boundary is considered to be "non-binding". In the absence of early trial stopping, the final primary analysis will be performed after approximately 180 OS events have been documented. There will be two interim analyses (IA) following a group sequential design:

- A futility IA will be performed after approximately 72 OS events (40% information fraction) have been documented.
- An efficacy IA will be conducted when approximately 135 OS events (75% information fraction) have been documented and when all subjects have been randomized.

Probability of Success (PoS) will be used to determine the futility boundary at the futility IA. PoS is defined as the marginal conditional probability of achieving statistical significance at either the efficacy interim or the primary analysis, given the phase II study [CMBG453B12201]

[redacted]

and phase III study [CMBG453B12301] data available at the time of the phase III study futility interim. It is calculated by averaging the conditional phase III power function (given the phase III data) over the posterior distribution for the log hazard ratio (log-HR) based on the available phase II and phase III data.

At the time of the futility IA, OS data available from the parallel ongoing phase II study [CMBG453B12201] will be used to formulate a robust meta-analytic-predictive (MAP) prior for the log-HR in phase III. If available, this prior will be used in the PoS calculation. The phase III study will be terminated for lack of efficacy at the futility IA if the PoS is less than 15%. There are three scenarios for the phase II data that will be available to inform stopping decisions at the time of the phase III study futility IA:

- If the futility IA occurs before CR rate analysis of [CMBG453B12201] study, no phase II study data will be used.
- If the futility IA occurs after CR rate analysis and before the PFS IA of [CMBG453B12201] study, OS data collected until CR rate analysis in phase II will be used.
- If the futility IA occurs after PFS IA of [CMBG453B12201] study, OS data collected until PFS IA in phase II will be used.

16.3.2 Statistical Models

16.3.2.1 Leveraging CMBG453B12201 data in robust MAP prior

Label the log-HRs underpinning [CMBG453B12201] and [CMBG453B12301] as θ_2 and θ_3, respectively. We will summarize the data accumulated by the time of the IA of the [CMBG453B12201] phase II study by the estimate of the log-HR and its standard error ($\hat{\theta}_2$ and se_2). Similarly, we summarize the data accumulated by the time of the phase III futility IA by the estimate of the log-HR and its standard error ($\hat{\theta}_3$ and se_3). Let d_i be the total number of OS events contributed from study i to the phase III futility analysis. Asymptotically, $\hat{\theta}_i \sim N(\theta_i, 4/d_i)$ so that the standard error of $\hat{\theta}_i$ is $se_i = \sqrt{4/d_i}$. Assuming the log-HRs underpinning the phase II and phase III studies are exchangeable, we can model the study-specific estimates using a Bayesian hierarchical random-effects model:

$$\hat{\theta}_i \mid \theta_i \sim N(\theta_i,\ se_i^2), \qquad i = 2,3$$

$$\theta_i \mid \mu, \tau \sim N(\mu, \tau^2), \qquad i = 2,3$$

$$\tau \sim HN(z^2)$$

We set z = 0.125, which is consistent with moderate between-study heterogeneity for a two-group (comparative) parameter (Neuenschwander et al 2016)

Given the observed [CMBG453B12201] phase II log-HR estimate ($\hat{\theta}_2$), we will fit the Bayesian meta-analytic model above and derive a MAP prior for θ_3, which we will approximate by a finite mixture of Gaussian distributions. To allow more rapid discounting of the phase II data in case of a prior-data conflict, we will use a robust version of the MAP prior. This will be a mixture of Gaussian distributions placing weight 0.9 on the MAP prior and weight 0.1 on a $N(0, 2^2)$ distribution, which is a weakly informative prior centered at the null with unit information standard deviation. Then, at the phase III futility IA, we will update the robust MAP

[redacted]

prior with the phase III log-HR estimate ($\hat{\theta}_3$), to obtain a posterior distribution for the log-HR in phase III, θ_3.

16.3.2.2 Simulating the phase II and phase III trials

Since the phase II data are not yet available, in order to evaluate the operating characteristics of the phase III study we simulate the [CMBG453B12301] and [CMBG453B12201] studies following the steps below.

We simulate individual OS patient data (time to event) from the phase II study assuming OS follows a piecewise exponential distribution on each arm. We simulate individual accrual time from a piecewise Uniform distribution, with an accrual rate of an average of 4 subjects per month in the first month, 8 subjects per month in the second month, 12 subjects per month in the third month, 16 subjects per month in the fourth month, and 20 subjects per month thereafter. We assume losses to follow-up of 10% per treatment arm per year. We simulate under the assumption that the phase III futility IA will occur after the CR rate analysis and before the PFS IA in phase II, so that the OS data collected until the CR rate analysis in phase II will be used. We analyze the phase II dataset using a log-rank test, accounting for administrative censoring. We estimate the phase II log-HR by U_{2L}/V_{2L}, where U_{2L} is the difference between the total number of observed and expected (under the null hypothesis) OS events in the MBG453 group in phase II and V_{2L} is the variance of the U_{2L} statistic. We approximate the standard error of the phase II log-HR estimate by $\sqrt{4/d_2}$. We use the estimate of the log-HR in phase II to create a robustified MAP prior for the log-HR in the phase III trial following the approach described in Section 16.3.2.1.

Similarly, we simulate individual patient data from the phase III study assuming OS times follow a piecewise exponential distribution on each arm. We deduce the dataset available at the time of the futility analysis taking into account administrative censoring. We estimate the phase III log-HR by U_{3L}/V_{3L}, where U_{3L} is the difference between the total number of observed and expected (under the null hypothesis) OS events in the MBG453 group in phase III at the time of the futility analysis, and V_{3L} is the variance of the U_{3L} statistic. We estimate the standard error of the phase III log-HR estimate by $\sqrt{4/d_3}$. Using Bayes Theorem; we update the robust MAP prior distribution for the log-HR in phase III with the phase III log-HR estimate. We generate Monte Carlo samples from the posterior distribution for the phase III log-HR thus obtained. We stop the phase III trial for futility if the posterior predictive probability of success is less than the decision threshold of 15%, that is, if

$$\int_{-\infty}^{\infty} \Pr(\text{Reject } H_0 \text{ in Ph3} \mid \hat{\theta}_3, \hat{\theta}_2, \theta_3)\, \pi(\theta_3 \mid \hat{\theta}_3, \hat{\theta}_2) \mathrm{d}\theta_3 < 0.15$$

where θ_3 is the log HR in phase III; $\pi(\theta_3 \mid \hat{\theta}_3, \hat{\theta}_2)$ is the posterior density for the phase III log-HR given the interim log-HR estimates from phase III and phase II (derived in Step 5). It is clear that given $\hat{\theta}_3$ and θ_3, the outcome of the phase III trial is conditionally independent of $\hat{\theta}_2$. Therefore, the futility stopping rule can be written as: stop for futility if

$$\int_{-\infty}^{\infty} \Pr(\text{Reject } H_0 \text{ in Ph3} \mid \hat{\theta}_3, \theta_3)\, \pi(\theta_3 \mid \hat{\theta}_3, \hat{\theta}_2) \mathrm{d}\theta_3 < 0.15$$

Writing the standardized test statistic at the phase III futility interim as $Z_{31} = \hat{\theta}_3\sqrt{d_3/4}$, we know that $\Pr(\text{Reject } H_0 \text{ in Ph3} \mid Z_{31}=z_{31}, \theta_3) = \Pr(Z_{32} \le l_2 \mid Z_{31} = z_{31}, \theta_3) + \Pr(Z_{32} > l_2, Z_{33} \le l_3 \mid$

[redacted]

$Z_{31} = z_{31}, \theta_3$), where Z_{32} and Z_{33} denote the standardized test statistics at the efficacy IA and final analysis, respectively. Here Pr(Reject H_0 in Ph3 | $Z_{31}=z_{31}, \theta_3$) is the conditional probability that the phase III trial will go on to reject H_0 at either the efficacy IA or the final analysis given the phase III data available at the futility interim and given the true log-HR in phase III is θ_3. We calculate PoS using Monte Carlo simulation. For i=1,..., N, we take the ith sample from the posterior distribution for θ_3 (denoted by $\theta_{3(i)}$) and calculate Pr(Reject H_0 in Ph3 | $Z_{31}=z_{31}$, $\theta_{3(i)}$). We then take the average of the N conditional powers. This average is the PoS which we compare with the PoS stopping threshold of 15%. In all of our evaluations, we have set N = 40,000.

16.3.3 Hypothetical scenarios

To illustrate the performance of the Bayesian model used to guide the futility decision making with PoS for MBG453 in combination with azacitidine, hypothetical data scenarios are displayed in the Table 16-4 below. In addition to the criteria based on PoS, the decision to stop the trial for lack of efficacy at the futility IA might be based on additional safety, PK or PD information.

Table 16-4 Futility interim decision recommended by PoS

PhII HR	PhIII HR	Posterior median	Conditional power under theta = delta	Effective sample size*	Critical HR**	PoS	Futility IA decision
Leverage PhII							
0.60	0.60	0.60	0.97	100.32	0.95	90.3%	Go
1.00	0.60	0.69	0.97	97.77	0.86	79.0%	Go
0.60	0.90	0.81	0.66	98.83	0.95	21.6%	Go
0.80	0.90	0.87	0.66	101.69	0.89	14.3%	No-Go
1.00	0.90	0.93	0.66	100.07	0.86	10.0%	No-Go
0.40	1.00	0.80	0.52	82.56	1.01	16.5%	Go
0.60	1.00	0.88	0.52	96.87	0.95	9.4%	No-Go
1.00	1.00	1.00	0.52	100.30	0.86	3.5%	No-Go
No PhII data							
-	0.60	0.60	NA	72	0.89	88.6%	Go
-	0.90	0.90	NA	72	0.89	14.4%	No-Go
-	1.00	1.00	NA	72	0.89	5.0%	No-Go

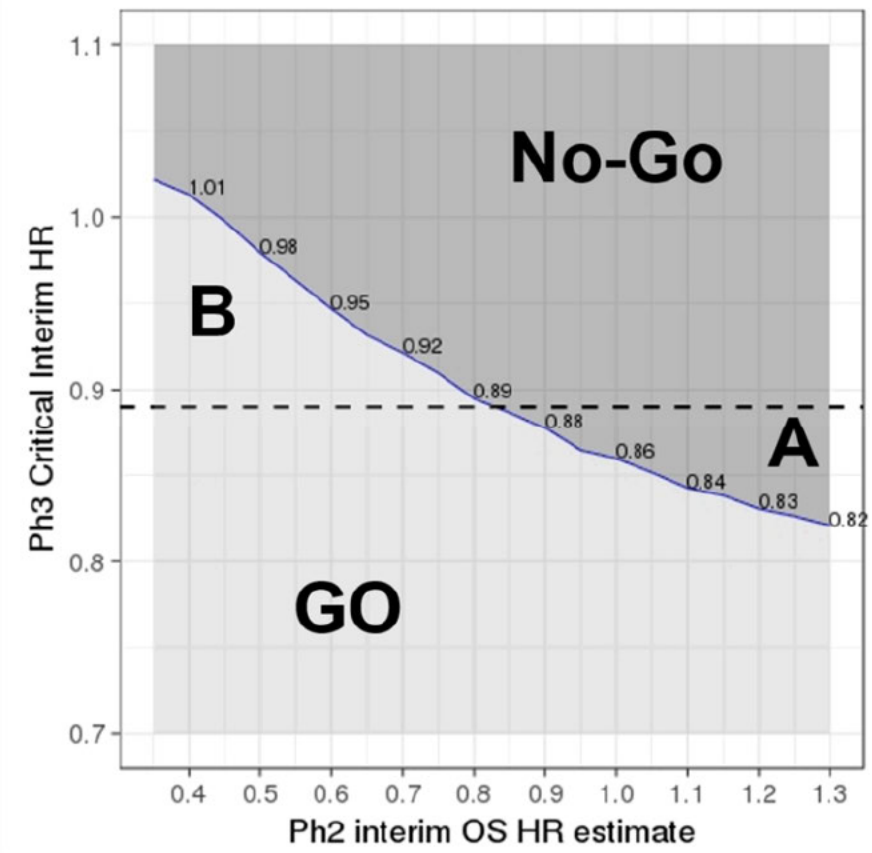
*Effective sample size means the number of OS events information

** Critical value for PoS=15% threshold

The decision rules at interim analysis based on the critical HR in phase III study as a function of the HR estimate in PhII are presented below in Figure 16-2.

[redacted]

Figure 16-2 Critical HR in Ph3 as a function of the HR estimate observed in Ph2 (PoS=15% threshold)



"No-Go" for stopping rule which leverages Ph2 data with PoS threshold = 15%

"Go" for stopping rule which leverages no Ph2 data with PoS threshold = 15%

Area A:

Method 1: Leverages Ph2 data with PoS threshold = 15% -- **No-Go**

Method 2: Group sequential design with threshold HR = 0.89 – **Go**

Area B

Method 1: Leverages Ph2 data with PoS threshold = 15% -- **Go**

Method 2: Group sequential design with threshold HR = 0.89 -- **No-Go**

16.3.4 Operating characteristics

The following operating characteristics were performed for difference true hazard ratios for phase II and phase III studies ranges from 0.6 to 1.0.

The futility threshold of PoS of 15% gives approximately 90.3% power, 2.2% type I error rate and corresponds to a HR of 0.89 for futility. These are marginal Operating Characteristics, i.e. averaging across the distribution of the phase II interim data.

[redacted]

Table 16-5 Operating characteristics

PhII HR	PhIII HR	(%)Trial stop at fut. IA	% Trial stop at fut. IA & success at eff. IA or primary	% Trial cont. at fut. IA & failed at eff. IA or primary	% trials cont. at fut. IA and success at eff IA or primary (i.e. the power).	Effective SS median (min-max)	# of PhII OS events med (min-max)
Leverage PhII							
0.60	0.60	3.1%	1.7%	6.6%	90.3%	94 (82.7-100.4)	28 (19-38)
0.80	0.60	4.6%	2.8%	6.2%	89.2%	95.3 (69.7-102)	32 (22-41)
0.60	0.80	26.0%	2.1%	43.1%	30.9%	93.6 (72.4-100)	28 (19-38)
0.80	0.80	32.3%	3.0%	37.7%	30.0%	96 (81.5-102.3)	32 (22-41)
1.00	0.80	37.4%	3.6%	33.2%	29.4%	97.3 (71.4-104.2)	35 (25-45)
0.80	1.00	67.2%	0.1%	30.5%	2.3%	95.7 (79-102)	32 (22-41)
1.00	1.00	73.4%	0.2%	24.4%	2.2%	97.9 (81.5-104.5)	35 (25-45)
No PhII data							
--	0.6	4.1%	2.2%	6.1%	89.8%	72	--
--	0.8	31.6%	2.4%	37.8%	30.6%	72	--
--	1.0	68.0%	0.1%	29.7%	2.3%	72	--

[redacted]